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GB virus C/hepatitis G virus infection in chronic hepatitis C patients with and without interferon-α therapy

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Abstract

GB virus C/hepatitis G virus (GBV-C/HGV) RNA, detected by polymerase chain reaction, and antibodies to the GBV-C/HGV envelope protein (anti-E2), detected by an enzyme-linked immunosorbent assay, were used to evaluate both the impact of GBV-C/HGV on the coexistent hepatitis C virus (HCV) infection and the course of GBV-C/HGV infection in chronic hepatitis C patients with and without interferon-α (IFN-α) treatment. Of the 162 chronic hepatitis C patients treated with INF-α, 17.9% were GBV-C/HGV RNA-positive and 18.5% anti-E2-positive (total exposure, 35.2%). Neither present nor past GBV-C/HGV infection had impact on the clinical features, HCV virological characteristics and response to IFN-α treatment in chronic hepatitis C patients. Among patients with ongoing HCV/GBV-C/HGV coinfection, 20.7% (6/29) in IFN-α-treated patients lost GBV-C/HGV RNA concomitant with anti-E2 seropositivity, which was significantly higher than 4.8% (2/42) in patients without INF-α treatment ($P < 0.05$). Based on multivariate analyses, the significant factors associated with clearance of GBV-C/HGV viremia combined with anti-E2 seropositivity were baseline anti-E2 seropositivity and IFN-α treatment. In summary, GBV-C/HGV did not alter the course of coexistent HCV. IFN-α treatment was effective in some patients against GBV-C/HGV and might facilitate anti-E2 seroconversion in chronic hepatitis C patients with GBV-C/HGV viremia. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: GB virus C/hepatitis G virus RNA; Anti-E2 antibody; Hepatitis C virus; Interferon

1. Introduction

Sequence comparisons of the GB virus C (GBV-C) and hepatitis G virus (HGV), identified as possible etiologic agents of viral hepatitis in humans, suggested that they are different isolates

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of the same virus, here referred to as GBV-C/HGV (Simons et al., 1995; Linnen et al., 1996; Leary et al., 1996). GBV-C/HGV has been reported in patients with posttransfusion (Linnen et al., 1996), acute, community-acquired hepatitis (Simons et al., 1995; Linnen et al., 1996) and fulminant hepatitis (Yoshiba et al., 1995), although its role in causing liver cell damage is still uncertain to date (Leary et al., 1996; Chen et al., 1998; Sheng et al., 1998; Tan et al., 1999; Yamada-Osaki et al., 1999). Studies on GBV-C/HGV have depended on the measurement of GBV-C/HGV RNA that reflects active HGV infection, by reverse transcription-polymerase chain reaction (RT-PCR) and on the detection of antibodies to the putative GBV-C/HGV envelope protein E2 (anti-E2), which serves as a recovery marker in acute and chronic GBV-C/HGV infection, by immunoassay systems (Tacke et al., 1997a,b). The combined use of these assays has allowed for more comprehensive studies on GBV-C/HGV infections, their natural course and the interaction with other hepatitis viruses (Yu et al., 2000a, 2001).

Dual infection of GBV-C/HGV and hepatitis C virus (HCV) is not uncommon. Of the HCV infected subjects, 10–20% were GBV-C/HGV viremic and 45–55% positive for anti-E2 antibodies in Japan and Europe (Tacke et al., 1997b; Enomoto et al., 1998; Tan et al., 1999). Several studies have indicated that interferon-α (IFN-α) treatment was effective on not only against HCV but also GBV-C/HGV in chronic hepatitis C patients coinfected with GBV-C/HGV (Martinot et al., 1997; Enomoto et al., 1998; Oshita et al., 1998). Clearance of GBV-C/HGV viremia combined with anti-E2 seroconversion 6 months after cessation of IFN-α treatment was observed in 15–30% patients. In other reports, however, IFN-α was shown to have a transient suppressive effect only on GBV-C/HGV viremia (Jarvis et al., 1998; Pawlotsky et al., 1998). In addition, spontaneous recovery from acute or chronic GBV-C/HGV infection concomitant with anti-E2 seroconversion, could occur in chronic hepatitis C patients during variable follow-up periods (Tacke et al., 1997b; Hwang et al., 1999; Tan et al., 1999; Yamada-Osaki et al., 1999). Thus, whether IFN-α therapy contributes to the clearance of both GBV-C/HGV viremia and anti-E2 seroconversion remains to be clarified.

To shed light on the effect of IFN-α therapy on GBV-C/HGV viremia, we conducted this retrospective study. Serum GBV-C/HGV RNA and anti-E2 were examined and followed in 162 chronic hepatitis C patients with IFN-α treatment to evaluate the effect of GBV-C/HGV coinfection on the clinicopathological features of HCV and its responsiveness to IFN-α therapy. To elucidate the effect of IFN-α on GBV-C/HGV viremia, a subset of patients with dual HCV and GBV-C/HGV infection were followed, and were compared to the natural course of dual HCV and GBV-C/HGV infection in patients without any antiviral therapy.

2. Materials and methods

2.1. Patients

One hundred and sixty-two Taiwanese patients, 93 males and 69 females, aged between 18 and 65 years (mean 45.7 ± 12.3 years) were enrolled in the study. All were positive for HCV antibodies (anti-HCV, second-generation, Abbott, North Chicago, IL) and serum HCV RNA, and negative for hepatitis B surface antigen (HBsAg, Abbott). The patients included 40 cases of chronic persistent hepatitis (CPH), 85 chronic active hepatitis (CAH) and 37 cirrhosis. The diagnosis of chronic hepatitis was made histologically based on standard criteria. Cirrhosis was diagnosed histologically or clinicopathologically. Forty-one patients (25.3%) had a history of blood transfusion. After they had given their informed consent, all patients were treated with recombinant IFN-α 2a ($n = 31$), IFN-α 2b ($n = 71$), or lymphoblastoid IFN-αn1 ($n = 60$) given intramuscularly. Three different regimens were followed: (1) 3 million units (MU) of IFN-α thrice a week for 24 weeks (low dose, $n = 21$); (2) 6 MU thrice a week for 24 weeks (medium dose, $n = 101$); and (3) 6 MU thrice a week for 24 weeks followed by 3 MU a week for 24 weeks (high dose, $n = 40$). The presence of HCV RNA in the serum was assessed every 3

months. Complete HCV responders were defined as patients showing normal alanine aminotransferase (ALT) levels and clearance of serum HCV RNA by nested RT-PCR at the end of the therapy and for 6 months after the cessation of therapy. All other patients were classified as HCV non-responders. Patients with GBV-C/HGV viremia before IFN-α therapy were followed for serum GBV-C/HGV RNA and anti-E2 antibodies every 3 months. Clearance of serum GBV-C/HGV RNA concomitant with anti-E2 seropositivity was defined as negativity of serum GBV-C/HGV RNA by nested RT-PCR at the end of the therapy and for 6 months after cessation of therapy accompanied appearance of anti-E2 antibodies 6 months after the cessation of therapy.

Three hundred chronic hepatitis C patients, who did not receive IFN-α treatment due to economic problem or worries about the efficacy and side effects of IFN-α treatment, were surveyed for serum GBV-C/HGV RNA by using nested RT-PCR with pooled serum samples (five in one) and then with individual serum sample for positive pooled samples. For patients positive for serum GBV-C/HGV RNA, anti-E2 antibodies were measured. Finally, 42 of 55 patients with dual HCV and GBV-C/HGV infections were followed for serum GBV-C/HGV RNA and anti-E2 antibodies every 3 months for 12 to 18 months without any antiviral therapy. These were 30 males and 12 females, aged between 19 to 64 years (mean 43.9 ± 12.1 years). All were positive for anti-HCV and serum HCV RNA, and negative for HBsAg. They included 13 cases of CPH, 18 CAH and 11 cirrhosis.

2.2. Detection/quantification of serum hepatitis C virus RNA and genotyping

Nested RT-PCR to detect serum HCV RNA was performed using 5′ untranslated region (UTR)-specific primers (Yu et al., 2000c). HCV genotypes 1a, 1b, 2a, 2b and 3a were determined by amplification of the core region using genotype-specific primers described by Okamoto et al. (1993). Serum HCV RNA levels were measured by using the branched DNA assay (Quantiplex HCV RNA 2.0, Chiron Corp., USA), performed strictly in accordance with the manufacturer's instructions (Yu et al., 2000b). The quantification range was 0.2 to 120 million equivalents of HCV RNA per ml.

2.3. Measurement of GBV-C/HGV RNA in serum

GBV-C/HGV RNA was detected by nested RT-PCR using primers targeting the 5′ UTR as described previously (Mukaide et al., 1997). Briefly, the total RNA was extracted from 140 μl of serum sample. After RT with Moloney murine leukemia virus reverse transcriptase, the first 30 cycles of PCR with primer pair 5gf2 and 5gr6 (94 °C for 1 min, 50 °C for 45 s, and 72 °C for 1 min) were performed, followed by the second 30 cycles of PCR with primer pair 5gf3 and 5gr4 (94 °C for 1 min, 55 °C for 45 s, and 72 °C for 1 min). PCR products were analyzed by gel electrophoresis using 3% agarose. In each PCR assay, two negative controls and one positive control were tested in addition to the samples of interest. In the RT-PCR assays for GBV-C/HGV RNA, all negative controls were negative and all positive controls were positive.

2.4. Sequencing of the 5′ untranslated region of GBV-C/HGV

Sequences of the amplified products of GBV-C/HGV were directly determined by using the dideoxynucleotide chain termination method (Dye terminator Cycle Sequencing FS Ready Reaction kit, Perkin–Elmer Cetus) with a DNA sequencer (ABI PRISM 373 DNA sequencer, Perkin–Elmer Cetus). The primer pair 5gf3 and 5gr4 was used as sequencing primers for both directions of the 5′ UTR. A phylogenetic tree was constructed using the Clustal method (Lasergene; DNASTAR, Inc. Madison, WI) based on the nucleotide sequences of the amplified 5′ UTR of GBV-C/HGV.

2.5. Measurement of anti-E2 antibodies in serum

Anti-E2 antibodies were measured by an en-

zyme linked immunosorbent assay from Boehringer Mannheim (GmbH, Germany), strictly according to the manufacturer's instructions (Tacke et al., 1997a,b).

2.6. Statistical analyses

Frequency was compared between the groups using the χ^2-test with Yates' correction or Fisher's exact test, and group means were compared using the t-test or ANOVA. Serum HCV RNA levels were expressed as the mean $\pm$ SD after logarithmic transformation of original values. Stepwise logistic regression was used to analyze factors associated with GBV-C/HGV anti-E2 seroconversion in chronic hepatitis C patients with GBV-C/HGV viremia.

3. Results

3.1. GBV-C/HGV viremia and anti-E2 antibodies in chronic hepatitis C patients

Of the 162 chronic hepatitis C patients before IFN-α therapy, 29 (17.9%) had GBV-C/HGV RNA and 30 (18.5%) had anti-E2 antibodies. Two were positive for both GBV-C/HGV RNA and anti-E2. Phylogenetic analysis of GBV-C/HGV RNA showed that 28 isolates clustered in Group 3; the remaining one was in Group 2 (Mukaide et al., 1997; Smith et al., 1997).

According to the status of GBV-C/HGV infection, 160 chronic hepatitis C patients were divided into three groups. Two patients positive for both GBV-C/HGV RNA and anti-E2 were not taken into analysis due to limited case number. There were 27 patients in the group with GBV-C/HGV RNA only; 28 in the group with anti-E2 only; and 105 in the group without either GBV-C/HGV RNA or anti-E2 (Table 1). There was no significant difference in the three groups as regarding age, sex, history of blood transfusion, liver histology, pretreatment serum ALT levels, HCV genotype, pretreatment HCV RNA levels, IFN-α preparation and regimen. The rate of HCV complete response did not differ among the three groups.

3.2. Clearance of GBV-C/HGV viremia concomitant with anti-E2 seropositivity in chronic hepatitis C patients with GBV-C/HGV viremia with and without IFN-α treatment

GBV-C/HGV markers were followed in 29 IFN-α-treated chronic hepatitis C patients concomitant with GBV-C/HGV viremia and 42 patients without IFN-α treatment. Sex, age, duration of follow-up, history of blood transfusion, liver histology, baseline serum ALT levels, HCV and GBV-C/HGV virologic characteristics did not differ between the IFN-α treated and untreated group (Table 2). The rate of clearance of GBV-C/HGV RNA concomitant with anti-E2 seropositivity was significantly higher in the IFN-α-treated group (6/29, 20.7%) than in the untreated group (2/42, 4.8%; $P < 0.05$). Among patients negative for anti-E2 at baseline, 14.8% of the treated patients (4/27) lost serum GBV-C/HGV RNA concomitant with anti-E2 seroconversion, which was higher than that of untreated patients (2.6%, 1/38; $P = 0.07$, borderline significance). Among patients positive for anti-E2 at baseline, the IFN-α-treated patients also had higher rate of clearance of serum GBV-C/HGV RNA combined with anti-E2 seropositivity than that of untreated patients (100% (2/2) vs. 25% (1/4); $P = 0.08$, borderline significance). Based on multiple logistic regression analyses, the significant factors related to clearance of serum GBV-C/HGV RNA concomitant with anti-E2 seropositivity were baseline anti-E2 seropositivity and IFN-α therapy (odds ratio and 95% CI: 2.63 and 2.21–335, 2.06 and 1.08–102, respectively).

In the 29 IFN-α-treated patients with dual HCV/GBV-C/HGV infection (Table 3), both two (100%) patients with baseline anti-E2 lost serum GBV-C/HGV RNA and remained anti-E2 seropositivity. By contrast, only four of 27 (14.8%) patients without baseline anti-E2 lost serum GBV-C/HGV RNA combined with anti-E2 seropositivity ($P < 0.01$). Sex, age, history of blood transfusion, pretreatment serum ALT levels, liver histology, HCV virologic characteristics, IFN-α preparation and regimen, and GBV-C/HGV variants were not related to the response of GBV-C/HGV to IFN-α therapy in patients with

dual HCV/GBV-C/HGV infection. In the 29 patients, four were negative for both markers of GBV-C/HGV 6 months after cessation of IFN-α therapy. However, serum GBV-C/HGV RNA reappeared later in two patients. The other two remained negative for both markers of GBV-C/HGV 12 months after cessation of IFN-α therapy. All of the six patients with GBV-C/HGV clearance and anti-E2 seroconversion were HCV non-responders.

4. Discussion

In the present study, the course of GBV-C/HGV was only investigated in patients with a concomitant infection with HCV. About one-third of the Taiwanese patients with chronic hepatitis C have been exposed to GBV-C/HGV. One half of them cleared the virus with anti-E2 positivity, indicating that spontaneous clearance of virus concomitant with humoral immune response

Table 1
Clinical characteristics and interferon-α response of chronic hepatitis C patients between the following three groups, according to the status of GBV-C/HGV infection

	GBV-C/HGV RNA (+) only *n* (%)	Anti-E2 (+) only *n* (%)	GBV-C/HGV RNA (−) and anti-E2 (−) *n* (%)
No. of patients	27	28	105
Sex (M/F)	18/9	15/13	58/47
Age (year)	42.8 ± 12.6	45.5 ± 11.4	46.2 ± 12.5
History of transfusion	8 (29.6)	7 (25.0)	26 (24.8)
Liver histology			
CPH ($n = 39$)	8 (29.6)	5 (17.9)	26 (24.8)
CAH ($n = 85$)	13 (48.2)	18 (64.3)	54 (51.4)
Cirrhosis ($n = 36$)	6 (22.2)	5 (17.9)	25 (23.8)
ALT levels (IU/L)	90.4 ± 75.8	96.8 ± 85.4	88.5 ± 73.8
HCV viral load (log)[a]	6.16 ± 0.70	6.06 ± 0.75	6.06 ± 0.68
HCV genotype			
1b ($n = 57$)	8 (29.6)	12 (42.9)	37 (35.2)
2a ($n = 53$)	15 (55.6)	9 (32.1)	29 (27.6)
2b ($n = 12$)	2 (7.4)	1 (3.6)	9 (8.6)
mixed ($n = 18$)	2 (7.4)	2 (7.1)	14 (13.3)
unclassified ($n = 20$)	0	4 (14.3)	16 (15.2)
IFN-α preparation			
IFN-α2a	6 (22.2)	7 (25.0)	18 (17.1)
IFN-α2b	11 (40.7)	13 (46.4)	46 (43.8)
IFN-αn1	10 (37.0)	8 (28.6)	41 (39.1)
IFN-α regimen			
Low dose	2 (7.4)	3 (10.7)	16 (15.2)
Medium dose	17 (63.0)	18 (64.3)	65 (61.9)
High dose	8 (29.6)	7 (25.0)	24 (22.9)
HCV complete response	8 (29.6)	11 (39.3)	37 (35.2)

CPH, chronic persistent hepatitis; CAH, chronic active hepatitis; ALT, alanine aminotransferase; IFN, interferon.
[a] Expressed as mean ± SD of log(equiv./ml).

Table 2
Comparison of clinical characteristics and GBV-C/HGV clearance combined with anti-E2 seropositivity in GBV-C/HGV viremic patients of chronic hepatitis C with and without interferon-α therapy

Group	With IFN-α therapy *n* (%)	Without IFN-α therapy *n* (%)
No. of patients	29	42
Sex (M/F)	20/9	30/12
Duration of follow-up (month)	14.1 ± 2.9	14.2 ± 2.5
Age (year)	43.9 ± 13.0	43.9 ± 12.1
History of transfusion	8 (27.6)	13 (31.0)
ALT levels (IU/L)	91.2 ± 73.4	88.0 ± 102.1
Liver histology		
CPH	9 (31.0)	13 (31.0)
CAH	13 (44.8)	18 (42.9)
Cirrhosis	7 (24.1)	11 (26.2)
HCV genotype		
1b	10 (34.5)	18 (42.9)
2a	15 (51.7)	15 (35.7)
2b	2 (6.9)	3 (7.1)
mixed	2 (6.9)	3 (7.1)
unclassified	0	3 (7.1)
Baseline HCV viral loads (log)[a]	6.16 ± 0.74	6.09 ± 0.69
GBV-C/HGV variant		
Group 2	1 (3.4)	1 (2.4)
Group 3	28 (96.6)	41 (97.6)
Baseline anti-E2		
Positive	2 (6.9)	4 (9.5)
Negative	27 (93.1)	38 (90.5)
GBV-C/HGV clearance combined with anti-E2 seropositivity[b]		
Yes	6 (20.7)	2 (4.8)
No	23 (79.3)	40 (95.2)

ALT, alanine aminotransferase; IFN, interferon.
[a] Expressed as mean ± SD of log(equiv./ml).
[b] Difference between two groups was significant ($P<0.05$).

to E2 could occur not uncommonly without antiviral treatment. Factors determining the outcome of GBV-C/HGV infection are not well known. Mode of transmission and age at infection may be important factors in determining persistent GBV-C/HGV infection and defective immune response to GBV-C/HGV (Chen et al., 1998). Recovery from GBV-C/HGV infection may occur after a variable number of years (Tacke et al., 1997b; Yamada-Osaki et al., 1999). The mechanisms allowing spontaneous recovery to take place after several years of persistent viremia remain unclear. In the current study, co-existence of serum anti-E2 at baseline was the most important factor associated with clearance of GBV-C/HGV viremia with persistent anti-E2 seropositivity in chronic hepatitis C patients with GBV-C/HGV viremia whether with or without antiviral therapy. These results showed that the host's immunity rather than other viral factors might be the key point to the clearance of GBV-C/HGV viremia. Anti-E2 was shown to be highly associated with GBV-C/HGV clearance and protection from reinfection (Thomas et al., 1998). Nevertheless, co-detection of GBV-C/HGV RNA and anti-E2 may occur for more than one year (Tacke et al., 1997b; Thomas et al., 1998). Clearance of serum GBV-C/HGV RNA may also occur without anti-E2 seroconversion (Sheng et al., 1998; Yamada-Osaki et al., 1999). Thus, existing data indicate merely that anti-E2 is a recovery marker of GBV-C/HGV infection and that the elimination of the virus may be effected by other effector mechanisms, e.g., cytotoxic T cells (Tacke et al., 1997b). Further studies are needed to assess the role of anti-E2 in neutralization.

The most important finding of this study was that the IFN-α treated group had a two-fold success rate of GBV-C/HGV clearance combined with anti-E2 seropositivity, as compared with the untreated group. These results indicate that IFN-α has a potential antiviral effect on GBV-C/HGV and may facilitate anti-E2 seroconversion in chronic hepatitis C patients with GBV-C/HGV viremia. Two of the ten patients with serum GBV-C/HGV RNA seronegativity at the end of IFN-α therapy had reappearance of serum GBV-C/HGV RNA one year later. Transient disappearance of GBV-C/HGV viremia during IFN-α treatment was also observed in previous reports (Martinot et al., 1997; Enomoto et al., 1998; Jarvis et al., 1998; Oshita et al., 1998; Pawlotsky et al., 1998), demonstrating the direct antiviral effects of IFN-α in suppressing GBV-C/HGV. In patients without co-existence of baseline anti-E2, a higher rate of GBV-C/HGV clearance with concomitant anti-E2 seropositivity was also noted in the IFN-α treated group compared to the untreated group. Al-

though the difference was of borderline significance due to the limited case numbers, these results suggest that immunomodulatory actions of IFN-α may also play an important role in facilitating clearance of GBV-C/HGV. Clearance of serum hepatitis B virus (HBV) DNA and seroconversion of antibody to hepatitis B e antigen after flare up of serum ALT levels during IFN-α treatment period indicated that immune modulation played an important role in the clearance of HBV DNA (Thomas and Foster, 1993; Main and Thomas, 1998). However, no

Table 3
Factors in relation to GBV-C/HGV clearance combined with anti-E2 seropositivity in 29 GBV-C/HGV viremic patients of chronic hepatitis C with interferon-α therapy

	n	GBV-C/HGV clearance combined with anti-E2 seropositivity 6 months after IFN-α therapy	
		Yes, $n=6$ (20.7%)	No, $n=23$ (79.3%)
Sex (M/F)	20/9	6/0	14/9
Age (year)	29	43.2 ± 12.8	46.7 ± 14.6
History of transfusion	8	3 (20.0)	5 (29.2)
Liver histology			
CPH	9	1 (16.7)	8 (34.8)
CAH	13	3 (50.0)	10 (43.5)
Cirrhosis	7	2 (33.3)	5 (21.7)
ALT levels (IU/L)		72.3 ± 43.4	96.1 ± 79.4
HCV genotype			
1b	10	3 (50.0)	7 (30.4)
2a	15	3 (50.0)	12 (52.2)
2b	2	0	2 (8.7)
Mixed	2	0	2 (8.7)
HCV viral load (log equiv./ml)		6.33 ± 1.00	6.12 ± 0.68
GBV-C/HGV variant			
Group 2	1	0	1 (4.3)
Group 3	28	6 (100)	22 (95.7)
Baseline anti-E2[a]			
Positive	2	2 (33.3)	0
Negative	27	4 (66.7)	23 (100)
IFN-α preparation			
IFN-α2a	6	1 (16.7)	5 (21.7)
IFN-α2b	12	3 (50.0)	9 (39.1)
IFN-αn1	11	2 (33.3)	9 (39.1)
IFN-α regimen			
Low dose	2	0	2 (8.7)
Medium dose	18	4 (66.7)	14 (60.9)
High dose	9	2 (33.3)	7 (30.4)
HCV response			
Complete responder	8	0	8 (34.8)
Non-responder	21	6 (100)	15 (65.2)

CPH, chronic persistent hepatitis; CAH, chronic active hepatitis; ALT, alanine aminotransferase; IFN, interferon.
[a] Difference between two groups was significant ($P<0.01$).

similar biochemical change was observed in the present study. Since liver might be not the major site of GBV-C/HGV replication in most patients (Berg et al., 1999), the enhanced host's immunity might not induce liver damage and flare up of ALT levels during IFN-α treatment in GBV-C/HGV viremic patients. The findings in the present study imply that both antiviral effects and immunomodulatory actions of IFN-α are important in the eradication of GBV-C/HGV. Further studies are needed to clarify the mechanism of responsiveness of GBV-C/HGV to IFN-α.

Dual infection of GBV-C/HGV and other hepatitis viruses is not uncommon. Co-infection of multiple hepatitis viruses might modify the clinical features of liver disease, such as the inhibitory action of viral replication in dual HBV and HCV infection (Koike et al., 1995). However, GBV-C/HGV was not observed to interfere with HCV replication and its hepatopathic effect in the present study. The response of HCV to IFN-α treatment was also not affected by the presence of GBV-C/HGV viremia and/or anti-E2 antibodies. Furthermore, in the IFN-α-treated patients, all the eight HCV complete responders did not have GBV-C/HGV clearance combined with anti-E2 seropositivity, nor were any of the six patients with GBV-C/HGV clearance combined with anti-E2 seropositivity HCV complete responders. The different virologic kinetics of GBV-C/HGV and HCV response to IFN-α underscores the importance of the virologic basis of the resistance to IFN-α.

In conclusion, approximately one-third of the chronic hepatitis C patients had been exposed to GBV-C/HGV, and half of them recovered from GBV-C/HGV infection with anti-E2 positivity. Both present and past coinfection of GBV-C/HGV had little impact on the hepatopathic effect of HCV and its response to IFN-α therapy. Anti-E2 was the most important factor associated with clearance of GBV-C/HGV viremia whether with or without antiviral therapy. IFN-α treatment was effective in some patients against GBV-C/HGV and might facilitate anti-E2 seroconversion in chronic hepatitis C patients with GBV-C/HGV viremia.

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