Conferences and Reviews

Hepatitis G Virus: Is it a Hepatitis Virus?

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Hepatitis G virus (HGV) and GB virus C (GBV-C) are two newly discovered viral agents, different isolates of a positive-sense RNA virus that represents a new genus of *Flaviviridae*. The purpose of this review is to analyze new data that have recently been published on the epidemiology and associations between HGV and liver diseases such as posttransfusion hepatitis, acute and chronic non-A–E hepatitis, fulminant hepatitis, cryptogenic cirrhosis, and hepatocellular carcinoma. The role of HGV in coinfection with other hepatitis viruses, the response to antiviral therapy, and the impact of HGV on liver transplantation are also discussed. HGV is a transmissible blood-borne viral agent that frequently occurs as a coinfection with other hepatitis viruses due to common modes of transmission. The prevalence of HGV ranges from 0.9 to 10% among blood donors throughout the world and is found in 1.7% of volunteer blood donors in the United States. The majority of patients infected with HGV by blood transfusion do not develop chronic hepatitis, but hepatitis G viremia frequently persists without biochemical evidence of hepatitis. Serum HGV RNA has been found in 0 to 50% of patients with fulminant hepatitis of unknown etiology and 14 to 36% of patients with cryptogenic cirrhosis. The association between HGV and chronic non-A–E hepatitis remains unclear. Although HGV appears to be a hepatotrophic virus, its role in independently causing acute and chronic liver diseases remains uncertain.

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Viral hepatitis is a major problem worldwide and is caused by five well-characterized etiologic agents.* Hepatitis viruses A, B, C, D, and E are distinct viruses whose molecular structure and disease associations are well known. All five viruses can cause acute hepatitis, but only hepatitis B, C and D can result in chronic infection. With the advent of precise serological and virological testing for all five viruses, it was recognized that 5 to 15% of patients with acute or chronic viral hepatitis were negative for all viral markers and had an illness operationally termed non-A–E hepatitis. A novel agent called hepatitis F virus was described as a new, enterically transmitted virus,[1] but this observation has not been confirmed and was likely a premature designation. Another hepatitis virus, the hepatitis G virus (HGV),[2] which appears to be the same virus as GB virus C (GBV-C),[3] has been identified, confirmed, and cloned. Two recent reviews on HGV[4,5] offered limited information on the clinical relevance of HGV in various diseases. The most recent information on HGV available in the literature, primarily in abstract form, constitutes the basis of this review. Hepatitis G virus, or GBV-C, infection has also been reported to be associated with various diseases such as aplastic anemia;[6,7] however, this review will focus mainly on the association of HGV with various liver diseases such as posttransfusion hepatitis, fulminant hepatitis, acute and chronic non-A–E hepatitis, and cryptogenic cirrhosis.

*See also the Editorial by Herbert L. Bonkovsky, "The Alphabet Soup of Viral Hepatitis: Is G a New Flavi(or) in the Mix?," on pages 49–50 of this issue.

Historical Perspective

Following the discovery of hepatitis C virus (HCV) in 1989,[8] it was recognized that there was a residual small percentage of community-associated and posttransfusion hepatitis cases caused by an unidentified viral agent. In addition, it had long been speculated that there were more than one non-A, non-B (NANB) transfusion-associated viral agents on the basis of chimpanzee cross-challenge studies and the observation that there was a chloroform-sensitive and a chloroform-resistant infectious agent.[9] Recent investigation led to the independent discovery of HGV[2] and GBV-C,[3] which were found to be different isolates of the same virus with >95% amino acid homology.[10]

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ABBREVIATIONS USED IN TEXT

CDC = Centers for Disease Control and Prevention
ELISA = enzyme linked immunosorbent assay
GBV-C = GB virus C
HBV = hepatitis B virus
HCV = hepatitis C virus
HGV = hepatitis G virus
NANB = non-A, non-B
NIH = National Institutes of Health
NS = nonstructural
ORF = open reading frame
PCR = polymerase chain reaction
RNA = ribonucleic acid
SGPT = serum glutamate pyruvate transaminase
UTR = untranslated region

A GB hepatitis agent isolated from serum obtained from a 34-year-old surgeon (whose initials are GB) during the third day of jaundice was serially passed in the experimental animal, *Sanguinus sp.* (tamarin). Using representational difference analysis to clone the nucleotide sequences from the serum of a tamarin infected with the GB hepatitis agent, investigators at Abbott Laboratories discovered two flavivirus-like genomes which were called GBV-A and GBV-B.[11,12] It was later determined that GBV-A and GBV-B were most likely nonhuman viruses that only infect tamarins.[13] Human sera from individuals considered to be "at risk for non-A–E hepatitis" were screened for antibodies that recognize GBV-A and/or GBV-B recombinant proteins. Immunoreactive sera were subjected to polymerase chain reaction (PCR) using degenerative oligonucleotides capable of amplifying a segment of the putative helicase gene from GBV-A, GBV-B, or HCV. A PCR product from a West African specimen revealed a novel virus-like nucleotide sequence that was named GBV-C, which is most likely derived from a human virus.[3]

Simultaneously, researchers at Genelabs, using an immunoscreening technique similar to the strategy that led to the discovery of HCV, discovered a flavivirus-like sequence from a patient with NANB hepatitis, provisionally called hepatitis G virus.[2] Molecular cloning was performed from the plasma of a US patient with NANB hepatitis obtained through the Centers for Disease Control and Prevention (CDC) Sentinel Counties Studies of Viral Hepatitis. The patient was initially thought to be HCV-negative by the first-generation immunoassay but was subsequently found by the second-generation assay and PCR to be positive for HCV. Therefore, the original sequence of HGV was isolated from a patient who was coinfected with HCV. The HGV was found to be very closely related to GBV-C and to belong to the family *Flaviviridae*. The newly discovered viruses will be referred to as either GBV-C or HGV based on the terminology used in original studies, but will generally be referred to as HGV in this review.

Hepatitis G Virus

The genome of HGV is a positive-sense RNA that has sequence and organizational similarity to other viruses within the *Flaviviridae* family.[2,14] The original HGV isolate contains a continuous open reading frame (ORF) preceded by a 5′ untranslated sequence of 458 nucleotides and followed by a 3′ untranslated region (UTR) of 315 nucleotides. The ORF encodes a polyprotein of 2873 amino acids with a number of characteristic motifs: a helicase motif, two chymotrypsin-like protease motifs and an RNA-dependent RNA polymerase

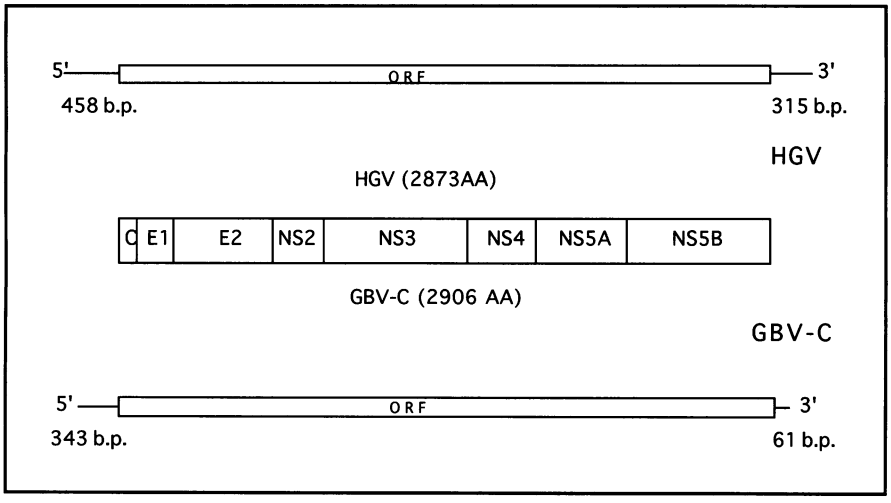

Figure 1. Genomic organization and comparison of the HGV and GBV-C. The viral genome has a single open reading frame (**ORF**) preceded by the 5′ untranslated region (**5′ UTR**) and followed by the **3′ UTR**. The open box represents the single ORF encoding the viral polyprotein, the thin line represents the 5′ UTR and 3′ UTR. Viral genome of HGV and GBV-C with sizes of the untranslated regions are shown in the upper and lower panel, respectively. The viral polyprotein encodes structural proteins, core (**C**) and envelope (**E1** and **E2**) followed by nonstructural regions (**NS2, NS3, NS4, NS5A,** and **NS5B**), and is shown in the middle panel with its size.

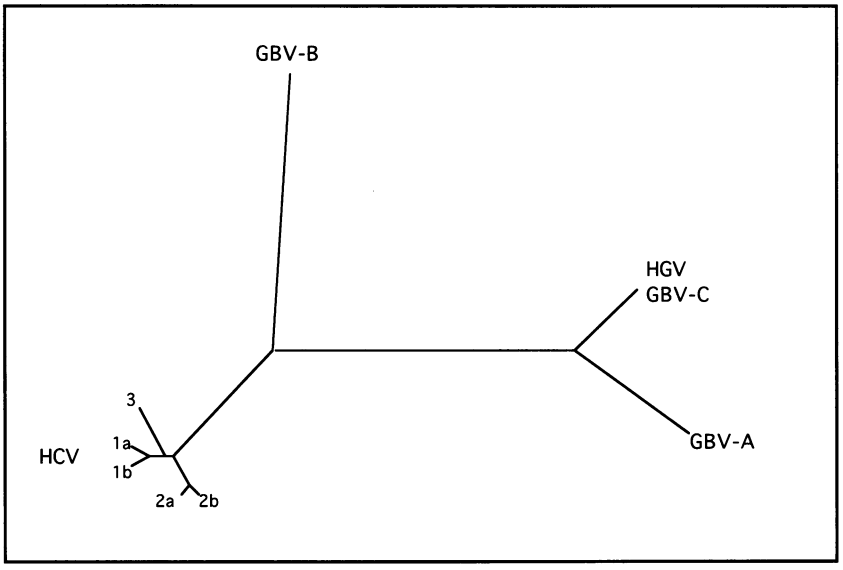

Figure 2. Unrooted phylogenetic analysis of the polyproteins of the GB agents (**GBV-A** and **GBV-B**), HGV, GBV-C, and various genotypes of hepatitis C virus (**HCV**). Modified from Leary et al.[14]

motif. The HGV genomic organization is similar to other members of the *Flaviviridae*, with the putative structural genes found at the 5′-end of the genome followed by putative nonstructural genes (Figure 1). The 5′ UTRs are highly conserved. The GBV-C is 9125 nucleotides in length, with a continuous ORF encoding a polyprotein of 2906 amino acids. This ORF is preceded by 343 nucleotides and followed by an additional 61 nucleotides of presumably untranslated sequence.[14] This polyprotein encodes an amino acid sequence motif consistent with a serine protease (in putative nonstructural 2 [NS2] region), a helicase (in putative NS3 region), and an RNA-dependent RNA polymerase (in the putative NS5B region). The GBV-C is more closely related to GBV-A (48% amino acid homology) than GBV-B (28% amino acid homology) or any of the HCV genotypes (29% amino acid homology with the HCV-1 isolate)[14] (Figure 2). The sequence similarity of HGV polyprotein is 43.8% identical to GBV-A, 28.4% identical to GBV-B, and 26.8% identical to HCV. The 331 nucleotides of the putative NS3 region of GBV-C show an 85.5% nucleotide identity and a 100% amino acid identity with the corresponding region of HGV. Alignment of the entire encoded polyprotein sequences of HGV with that of GBV-C shows 85% homology at the nucleic acid level and 95% at the amino acid level.[10] Therefore, these two viruses should be considered as different isolates of the same virus. Since this newly discovered virus is distinct from all other known flaviviruses including HCV, it is felt to form a new genus in the *Flaviviridae* family (Figure 2).

There is genetic heterogeneity among isolates from different geographic regions.[15–18] Phylogenetic analysis of the 5′ noncoding region of 146 HGV isolates from 16 different countries showed that there were three major subtypes: GBV-C and HGV as the prototype of two subtypes, and a new subtype commonly found in Asia.[15] Analysis of the 5′ noncoding region of HGV isolates from sera of Japanese patients showed that the degree of genetic differences between the Japanese isolates was similar to the subtype differences found in HCV; but when the Japanese isolates were compared with the prototypes, the degree of genetic differences corresponded to that found between different HCV genotypes.[16] The average similarity of the putative helicase region (NS3 region) of 21 Taiwanese GBV-C isolates to those from West Africa, East Africa, Canada, and the US were 83, 85, 78, and 82%, respectively.[17] All the Taiwanese isolates could be further classified into at least three groups. Therefore, there is genetic heterogeneity of HGV isolates from around the world, and HGV can probably be grouped into genetically distinct genotypes and subtypes as in the case of HCV. The significance of this genetic heterogeneity has yet to be determined but might explain the different rate of diseases associated with HGV in various studies.

Diagnosis of HGV Infection

Until the development of a serological assay from a highly-conserved region of HGV, infection can only be diagnosed by PCR assay to detect the viral RNA in serum. Since this assay detects only viral RNA, it will not be able to detect past infection as in the case of an antibody assay. In addition, conditions used for storage of serum are probably important since RNA is unstable. Sensitivity of the PCR assay will also depend on the choice of the PCR primers. The original primer set used by researchers from Genelabs were sequences derived from the putative NS5a region, and the PCR assay using these primers has a sensitivity of 200 copy equivalents

per milliliter of serum/plasma.[2] The primers that were developed by Simons et al.[3] were based on sequences from the putative NS3/helicase region. Using consensus oligonucleotide primers from the most highly conversed regions derived from eight GBV-C isolates, Leary et al.[19] were able to detect GBV-C RNA from 10 of 76 (13.2%) patients with non-A–E hepatitis compared with only four (5.3%) patients using a primer set and methods originally described by Simon et al.[3] This study clearly demonstrates the importance of primer selection and PCR protocols. A commercial PCR kit for detection of HGV RNA is available in Europe but not in this country (Hepatitis G virus probe set, Boehringer Mannheim GmbH, cat no. 1 782 720).

An enzyme-linked immunosorbent assay (ELISA) for detection of antibodies to recombinant HGV putative envelope protein E2 was recently described as a potential serological marker for immunity to HGV infection.[20] Antibodies to E2 were found in 9% of 80 healthy German blood donors, all of whom were HGV RNA negative. Antibodies to E2 were found in 41 of 99 intravenous drug users in Germany, but only four were viremic. Another 34 HGV RNA positive intravenous drug users were antibody negative. Among 11 Japanese patients with acute posttransfusion hepatitis (seven with HCV, three with hepatitis B virus [HBV] and one with non-A–E hepatitis) who were HGV RNA positive, all were initially antibody negative. Two of the four patients that subsequently developed antibodies to E2 became HGV RNA negative. These data suggest that antibodies to E2 might be a serological marker for diagnosing recovery from HGV infection, but further studies are necessary. Detection of HGV RNA by PCR remains the only established test for diagnosis of HGV infection.

Table 1.—*Prevalence of Serum HGV/GBV-C RNA Among Blood Donors*

Country	%
Japan	0.9
Spain	1.4–4.6
UK	3.2
Taiwan	4.2
Brazil	10
Australia	
Normal SGPT	4
Raised SGPT	5
US	
Accepted donations	1.7
Rejected donations (SGPT >45 IU/ml)	1.5

Epidemiology

Blood Donors

The prevalence of hepatitis G viremia among blood donors ranges from 0.9 to 10% (Table 1). Smaller series tend to report higher prevalence rates, which might reflect patient selection bias. Serum HGV RNA was detected in 1.7% of 779 consecutive U.S. volunteer blood donors with normal serum glutamate pyruvate transaminase (SGPT) levels. In contrast, HGV RNA was found in 11 (1.5%) of 709 donors who were rejected due to SGPT elevation.[2] In Queensland, Australia, HGV RNA was found in four of 100 blood donors (4%) with normal SGPT levels and in one of 20 (5%) with raised SGPT levels.[21] All 120 tested negative for antibodies to HCV, HIV-1, HIV-2, HTLV, and hepatitis B surface antigen and did not fall into any "at risk" group. One of the five HGV RNA positive patients was found to be HGV RNA negative on a prior plasma sample. His SGPT remained normal, and he had no identifiable risk factors for HGV infection. HGV has been detected in blood donors from other parts of the world with prevalence rates of 0.9% (4/448) in Japan,[22] 1.4% (14/1000)[23] and 4.6% (6/129)[24] in Spain, 2% (4/200) in Taiwan,[25] 3.2% in Edinburgh, UK,[26] 4.2% (21/500) in France,[27] and 10% (12/120) in Brazil[28] (Table 1). (The high 10% prevalence rate in Brazil, however, was based on the screening of only 120 blood donors.)

Using recombinant proteins from the putative core and NS genes NS3, NS4, and NS5 regions of GBV-B and nonstructural gene of GBV-A, researchers at Abbott Laboratories found the seroprevalence rate among US volunteer blood donors to be 1.2% (12/960) and 0.3% (3/860), respectively.[3] None was reactive for both viruses. Since GBV-A and GBV-B are nonhuman pathogens, these findings most likely represent cross-reactivity with proteins encoded by another related virus such as GBV-C. Serum GBV-C RNA was detected in only seven of 42 GBV-A and/or GBV-B seropositive West African samples. GBV-A or GBV-B RNA was not detected by PCR in any of the sera of 30 blood donors, 40 hemophiliacs, 30 intravenous drug users, 40 patients with chronic HBV/HCV infection, or 18 patients with acute or chronic non-A–E hepatitis.[29] Many of these patients were coinfected with HGV.

Transmission

HGV is a bloodborne virus that is parenterally transmitted. The strongest evidence that HGV is parenterally transmitted comes from prospective studies of posttransfusion hepatitis, in which other viral agents are excluded. HGV can be detected in sera of patients who were previously HGV negative after transfusion of blood from HGV positive donors. Sequence analysis of the NS3 region of HGV from two implicated donor and recipient pairs have shows striking sequence similarity (98 and 100%).[30]

The prevalence of HGV in populations exposed to multiple blood products and in intravenous drug users

has also been shown to be high. HGV was found in 5.4–18.6% of hemophiliacs[2,31,32] and 18% of anemic patients requiring multiple transfusions.[2] The majority of hemophiliacs who were HGV RNA positive were also coinfected with HCV (up to 75%).[33] The prevalence of HGV infection among patients on hemodialysis ranged from 3.1% in Japan[22] to 26% in Spain.[24] Serum HGV RNA was found in 12.5% of 120 hemodialysis patients in the US,[34] similar to the percentage in France.[35] Most patients who were infected with HGV/GBV-C alone had normal SGPT levels.[22,35] Serum HGV RNA was detected in 17 of 63 (27%) HCV RNA positive hemodialysis patients (Umlauft et al., unpublished observation). One study[22] found that 12 of 16 GBV-C RNA positive patients on maintenance hemodialysis had a history of transfusion, and GBV-C RNA was first detected 3 to 20 weeks after blood transfusion. Infection with GBV-C tended to persist in hemodialysis patients, and GBV-C disappeared from only one of eight patients followed for 7 to 16 years.

Among intravenous drug users, serum HGV RNA was found at rates of 33% in Europe,[2] 35% in Switzerland,[36] and 43% in Japan.[37] A study from the Los Angeles area found HGV RNA in only 12 of 124 (9.6%) intravenous drug users, and 11 of the 12 were coinfected with HCV.[34] In another study, up to 97% of the serum HGV RNA positive intravenous drug users were coinfected with HCV.[36]

Vertical transmission has also been reported. Three of nine babies born to HGV positive mothers became HGV RNA positive as assessed by PCR. One of the three was coinfected with HCV and the other two were coinfected with HIV.[38] In another case report from a HGV positive mother, the cord blood was negative and sera from the newborn at 4 and 6 weeks of age were HGV positive, suggesting that the infection occurred perinatally.[39]

There is currently no information on other modes of transmission. However, as in the case of HCV, many HGV positive patients have no identifiable parenteral risk factor.

Table 2.—*Prevalence of Serum HGV/GBV-C RNA in Patients With Various Liver Disease*

Liver Disease	%
Posttransfusion non-A–E hepatitis	12.5–15
Community-acquired acute non-A–E hepatitis	0–35
Fulminant hepatitis	0–50
Cryptogenic cirrhosis	14–36
Hepatocellular carcinoma	
HGV alone	8
HGV/HBV or HCV/HBV coinfection	4–12
Coinfection	
HGV/HBV	10–17
HGV/HCV	11–19

Associations of HGV with Liver Diseases

The association of HGV with liver diseases is based on prevalence of serum HGV/GBV-C RNA in such patients in some studies. The range of prevalence of HGV viremia in patients with various liver diseases is summarized in Table 2.

Posttransfusion Hepatitis (PTH)

Hepatitis C virus has been found to be the major viral pathogen that accounts for posttransfusion NANB hepatitis. The incidence of transfusion-associated hepatitis has markedly decreased with the screening of all potential donors for antibody to HCV (anti-HCV). There is always a group of patients in posttransfusion hepatitis studies whose illness cannot be attributed to hepatitis A, B, or C. In the National Institutes of Health (NIH) prospective PTH study, for example, 12% were non-A, non-B, non-C, suggesting that there was another transmittable viral agent.[40] The pursuit of such an infectious agent led to the discovery of HGV. HGV was isolated from the serum of one such patient although the patient was subsequently found to be coinfected with HCV (see discussion above).[2]

Although HGV is clearly a parenterally transmitted virus, its role as a cause of PTH is uncertain. There is a poor correlation between the presence of virus and chronic liver disease. Patients who develop chronic PTH are invariably coinfected with HCV, and chronic hepatitis correlates closely with HCV infection. In a large prospective study of PTH in Canada, the prevalence of HGV positivity by PCR in non-A–C PTH was 15% (3/20), or three in 4,588 blood recipients.[41] None of the three patients progressed to chronic liver disease, but HGV RNA persisted in one of the patients 5 years after recovery from PTH. Another prospective study of PTH showed that 40 of 400 patients who underwent cardiac surgery were GBV-C positive[25]: six were HGV positive before surgery, with five remaining viremic. Out of the 34 patients who became GBV-C positive after surgery, seven were coinfected with HCV and two were coinfected with HCV and HTLV-1. These 34 patients received blood products from a significantly higher number of donors than those not infected with GBV-C. The 25 recipients who became infected with GBV-C alone had a low mean peak serum SGPT of 31 IU/l. In this group, three had mild SGPT elevation (less than twofold the upper limit of normal), and two had peak SGPT levels of 101 and 123 IU/l, respectively, during the 6-month follow-up. All the patients who were infected with GBV-C alone were asymptomatic without evidence of hepatitis in the follow-up period of 1 to 8 years despite the persistence of GBV-C of up to 8 years. Serum GBV-C RNA occurred as early as 1 week after transfusion. The laboratory data and clinical course in the seven HCV coinfected recipients were similar to those infected with HCV alone. GBV-C was detected in only one of eight (12.5%) patients with non-A–E PTH. The risk of GBV-C transmission was esti-

mated to be approximately 0.46% per donor but rarely caused posttransfusion hepatitis. In fact, among all the cases of PTH that were felt to be associated with HGV viremia, the majority of studies[25,41-43] did not reveal progression to chronic hepatitis.

A prospective study of transfusion-associated hepatitis from the NIH showed that HGV RNA was found in nine of 79 patients with transfusion-associated NANB hepatitis, with six patients coinfected with HCV.[44] The disease in the three patients with HGV RNA as the only identifiable viral marker was mild, and only one remained persistently viremic with elevated SGPT levels for 4 years before dying from unrelated causes. The hepatic injury in the HCV/HGV coinfected patients was not different from the disease in those infected with HCV alone. An additional 12 patients with minor SGPT elevations that did not meet the study criteria and in 14 patients with no hepatitis were also HGV RNA positive. There was no significant difference in the proportion with HGV infection among the transfusion recipients with or without hepatitis. Therefore, most acute HGV infection associated with transfusion occurred without evidence of hepatitis. HGV infection, however, was found to be associated when compared with controls.

Therefore, even though it is well-documented that HGV is transmitted through blood, it is rarely a cause of PTH. There has been a decline in the incidence of PTH with the introduction of second-generation assays for screening of HCV, and in several recent studies, the incidence of posttransfusion SGPT elevation was no different from the nontransfused control population.[45,46] This suggests that some of these PTH cases represent "background hepatitis" or nonviral etiologies related to perioperative events.

Acute Community-Acquired Non-A-E Hepatitis

The evidence that there might be another viral agent accounting for community-acquired non-A–E hepatitis is stronger than in the case of PTH. Data from the CDC showed that only 82% of the NANB community-acquired acute hepatitis in the sentinel counties was caused by HCV.[47] A study from Greece showed that 47% of community-acquired NANB hepatitis is anti-HCV negative.[48] In Spain, 19% of acute hepatitis was classified as non-A–E.[49] Since hepatitis D always exists as a coinfection with HBV and hepatitis E virus is rarely a cause of acute hepatitis except in certain geographic areas such as India, all these non-A, non-B, non-C hepatitis cases are considered to be non-A–E hepatitis. A recent study found a very high prevalence of GBV-C in a group of Italian patients with hepatitis of unknown etiology.[50] Serum GBV-C RNA was found in 11 of 31 (35%) patients with acute non-A–E hepatitis and in seven of 18 (39%) with chronic hepatitis. Among 18 patients who were GBV-C positive, only one had a history of transfusion and three had used intravenous drugs. The lack of serum samples prior to the onset of disease preclude a definitive link between GBV-C infection and the onset of hepatitis.

Of the 38 patients identified as having community-acquired non-A–E hepatitis in four U.S. sentinel counties from 1985 to 1993, five (13%) were HGV RNA positive at the time of their acute illness. Four of the five remained HGV RNA positive over a follow-up period of 2–9 years, and none developed chronic hepatitis.[2] A follow-up study[51] showed HGV RNA in 25% of 100 patients with hepatitis A, 32% of 100 patients with hepatitis B, 20% of 116 patients with hepatitis C, but only 9% of 45 patients with non-A–E acute community-acquired hepatitis. The four patients with HGV alone had a median SGPT of 1680 IU/l (range, 200–3240 IU/l), a median bilirubin of 9.6 mg/dl (range, 0.6–30.9 mg/dl), and a median age of 27. The clinical characteristics of the acute illness were similar for patients with HGV alone and those with hepatitis A, B, or C with or without HGV infection. and HGV coinfection did not affect the clinical course. Chronic hepatitis developed in 60% of patients with HCV infection alone, compared with 61% of the HCV-HGV coinfected group. None of the HGV group alone developed chronic hepatitis even though three (75%) were persistently HGV positive for a follow-up period of 1 to 9 years. Based on the findings of this study, it was estimated that 0.3% of acute viral hepatitis may be infected with HGV alone.Therefore, HGV is not a major cause of acute community-acquired hepatitis in the US. Similarly, none of the 29 Japanese patients with acute non-A–C hepatitis was HGV RNA positive.[52]

HGV Coinfection with Other Hepatitis Viruses

Most of HGV infection occurs in the setting of coinfection with other hepatitis viruses such as HBV and HCV. This coinfection is probably related to similar modes of transmission. However, HGV appears to have little impact on the course of infection, and the clinical course is largely determined by the coinfecting virus. In Europe, HGV was found to coinfect seven of 72 (10%) patients with chronic HBV, and 18 of 96 (19%) patients with chronic HCV.[2] HGV coinfection was found in 11% of 99 US patients with chronic HCV infection, and the coinfection was not associated with detectable differences in viral load, HCV genotype, demographic features, or histological severity of liver disease.[53] The clinical course of seven posttransfusion GBV-C and HCV coinfected patients was similar to those infected by HCV alone.[25] Tanaka et al.[54] found that 21 of 189 (11%) Japanese patients with chronic hepatitis C were coinfected with HGV and found no difference between this group and those who had HCV infection alone in terms of clinical presentation (liver enzyme elevation, liver histology, history of transfusion), HCV RNA levels, or response to interferon therapy. The coinfected patients were generally younger.[54,55] Serum HGV RNA levels also decreased during interferon therapy, but only two of nine patients studied had a sustained response. The effects of interferon on GBV-C and HCV were independent.[54,55,81]

Marrone et al.[56] found HGV RNA in 18 (17%) of 104 patients with chronic hepatitis B, but found little effect of HGV infection on the course of hepatitis B or

response to interferon therapy. During interferon therapy, HGV RNA became undetectable in all 13 serially tested patients, but levels returned to pretreatment values after interferon was stopped.

In summary, serum HGV RNA is found in approximately 10–20% of patients with chronic hepatitis B or C infection but has little or no impact on the clinical course or response to interferon therapy.

Fulminant Hepatitis

Thirty to fifty percent of fulminant hepatitis cases from the US are NANB hepatitis,[57,58] suggesting the presence of another infectious agent that causes fulminant hepatitis. HCV was found to be an unusual cause of fulminant NANB hepatitis, and some cases actually represented serology-negative HBV infection.[59] A togavirus-like particle has also been found in some patients with NANB fulminant hepatitis.[60]

Yoshiba et al.[61] found GBV-C RNA in the serum of three of six Japanese patients with fulminant hepatitis of unknown etiology. All six patients were seronegative for all known hepatitis viruses, and five of the six eventually died of hepatic failure. All six patients were also subsequently shown to be HBV and HCV negative by PCR.[18] Of the three patients who were GBV-C positive, one had a history of transfusion, one was a nurse, and one had a history of acute self-limited NANB hepatitis. Kuroki et al.,[62] however, were unable to detect GBV-C from seven Japanese patients with fulminant hepatitis without any history of transfusion or acute hepatitis. All seven patients were seronegative for hepatitis A–D and were PCR negative for HBV, HCV, and HEV. One of the seven patients was GBV-C negative on admission, but one sample taken after transfusion was positive. As with the other series, all seven patients except the last case (who became GBV-C positive) died from hepatic failure. Several larger series from Japan found GBV-C/HGV to be uncommon among Japanese patients with fulminant hepatitis of unknown etiology. Serum HGV/GBV-C RNA was not detected in series of 26[63] and 10[64] Japanese patients with fulminant hepatitis. The study by Ishikawa et al.[52] found HGV RNA in only one of 21 patients with fulminant hepatitis, and this patient was also one of the four patients with fulminant hepatitis who were HCV RNA positive.

Data from the National Institute of Diabetes and Digestive and Kidney Diseases Liver Transplant Database showed that nine of 39 (23%) US patients with fulminant hepatic failure were HGV RNA positive before transplant.[65] There was no significant difference in the clinical and biochemical features between the HGV positive and negative groups. Most HGV RNA positive patients pretransplant remained positive at follow-up. However, most of the HGV PCR positive patients posttransplant acquired the infection de novo. Munoz et al.[66] found HGV RNA in 13 (36%) of 36 US patients with non-A–C fulminant hepatitis.

Among 131 patients admitted to a liver transplant unit in Scotland for fulminant hepatitis from 1992 to 1995, only five of 23 consecutive patients with non-A–E fulminant hepatitis were GBV-C RNA positive.[26] All five were GBV-C RNA positive using primers from the highly conserved 5′ noncoding region, but only four of the five were positive with primers from the NS3 region. All five patients were young (mean age 21) with relatively short duration of disease (mean of 25 days) and mean SGPT peak of 729 IU/l (range, 335–1494 IU/l). All five patients had received blood products during their hospitalization prior to testing positive for GBV-C RNA. Only two patients had sera available after the onset of hepatitis but prior to transfusion and both were negative for GBV-C RNA. This suggested that patients might be infected through transfusion after the onset of hepatitis. Two of the five patients died and two underwent liver transplantation. One patient who underwent liver transplantation was GBV-C RNA negative in a 5-month follow-up sample. One of the two patients who were initially GBV-C RNA negative recovered from fulminant hepatitis and was GBV-C RNA negative when retested 1 year later. This study suggests that GBV-C is unlikely to be a cause of fulminant hepatitis.

Studies from Germany found GBV-C RNA in one of 12 (8%)[67] and 12 of 24 (50%)[68] patients with fulminant hepatic failure. HGV RNA was detected in six of 21 (28%) Spanish patients with idiopathic fulminant hepatitis.[69] It is not clear if the wide differences in the incidence of HGV infection in patients with fulminant hepatitis from various series (0 to 50%) is related to differences in the genomic heterogeneity of HGV[15–18] or

Table 3.—*Prevalence of Serum HGV/GBV-C RNA in Liver Transplant Recipients*

Underlying Liver Disease	No. of Patients	HGV/GBV-C RNA Positive	
		Pretransplant %	Posttransplant %
Cryptogenic cirrhosis	14	36	71
Cryptogenic cirrhosis	45	20	67
Cryptogenic cirrhosis	70	16	54*
Fulminant hepatitis	39	23	

*54% of 69 patients who were HGV RNA negative before liver transplant for cryptogenic cirrhosis or fulminant hepatitis became HGV RNA positive posttransplant.

sensitivity of the PCR assays.[19] Most of these studies are retrospective, and the PCRs were performed on stored serum, which might have effects on the reliability of HGV RNA by PCR.

Cryptogenic Cirrhosis

Some patients who have chronic hepatitis and cirrhosis of unknown etiology may undergo liver transplantation. The reported prevalence of HGV in general appears to be related to the severity of liver disease. None of 26 Japanese patients with non-B, non-C chronic hepatitis was HGV RNA positive.[70] GBV-C RNA was found in two (6%) of 32 patients with cryptogenic chronic liver disease without cirrhosis[71] but in two of 14 (14%) patients with cryptogenic cirrhosis.[72] Among patients with advanced cryptogenic cirrhosis requiring liver transplantation, the prevalence of HGV before liver transplantation was 11 of 70 (16%)[65] and four of 19 (22%)[73] in the US and five of 14 (36%) in Italy.[74] The prevalence was much higher after liver transplantation (see discussion below).

HGV Infection in Liver Transplantation

Most patients who are serum HGV RNA positive before liver transplantation remain positive after transplant (Table 3). However, most HGV infections posttransplant are acquired de novo and are most likely related to the use of blood products at the time of surgery. In an Italian study, HGV RNA was found in five of 14 (36%) patients with cryptogenic cirrhosis before liver transplant, but was detected in 10 patients (71%) after transplant.[74] All patients who were HGV positive before liver transplantation had persistent infection posttransplant. Similarly, the prevalence of HGV RNA was found to be 20% in patients with cryptogenic cirrhosis before liver transplant but increased to 67% posttransplant.[75] In a group of 69 patients with either cryptogenic cirrhosis or fulminant hepatitis who were HGV negative before liver transplant, 38 or 69% became positive after transplant.[65] However, there appeared to be no association between HGV infection and patient survival,[76] graft survival,[65] or posttransplant hepatitis.[76] As with HCV, the mean HGV RNA level as determined by bDNA assay was significantly higher at 1 year posttransplant than the mean pretransplant titers.[73] Therefore, HGV infection was very common with liver transplantation, and viremia usually persisted after liver transplantation in patients who were HGV RNA positive before liver transplantation. However, HGV infection by itself has little or no impact on the graft or posttransplant course.

Hepatocellular Carcinoma

Serum HGV RNA has been found in patients with hepatocellular carcinoma (HCC). HGV RNA was found in only one of 28 HCV-infected patients with HCC.[77] Among patients transplanted with HCC, HGV RNA was found in four of 34 patients of whom three were coinfected with HCV and one was coinfected with HBV.[78] GBV-C RNA was found in 11 of 111 (10%) cases of HCC in Japan, but 10 of 11 were coinfected with HCV and one with HBV. HGV RNA was found as the only infectious viral agent in seven (8%) of 85 Austrian patients with HCC.[79] Since the majority of patients with HCC were coinfected with either HBV or HCV, the role of HGV in the etiology of HCC is unclear. Therefore, with the exception of the Austrian study,[79] HGV is unlikely to be a major etiologic agent of HCC.

Response of HGV to Antiviral Therapy

There are no data on treatment of patients who are infected with HGV alone, since the role of HGV as a cause of chronic viral hepatitis has yet to be determined. Studies of patients coinfected with HCV who were treated with interferon showed that HGV is sensitive to interferon therapy. The responsiveness of HCV and HGV appeared to be unrelated, and biochemical response to interferon therapy was correlated with HCV alone.[53-55,81] As in the case of HCV, most of the decrease or disappearance of HGV RNA during interferon therapy was transient, and reappearance of HGV RNA was very common. Tanaka et al.[54] found that only two of the nine HGV/HCV coinfected patients studied had a sustained HGV response to interferon therapy. Neither patient cleared HCV RNA. Three of the patients who had sustained response to HCV did not clear HGV RNA, but SGPT levels remained normal despite reappearance of HGV RNA after interferon therapy. Another study showed that HGV RNA level decreased and even become undetectable during therapy among two patients coinfected with HBV and six patients with HCV treated with interferon. However, HGV RNA returned to pretreatment levels in all patients after interferon was stopped, including the HCV coinfected patient with sustained response with normal SGPT.[29] We found similar results in a group of HGV/HCV coinfected patients on hemodialysis who were treated with interferon. All 10 coinfected patients were HGV RNA negative at the end of interferon therapy but only three remained so after 1-year follow-up, and the response was independent of that of HCV (unpublished observation). In contrast to interferon, ribivarin has little effect on serum HGV RNA levels.[80,81]

Summary

This paper reviews current information on the newly discovered viral agent, HGV. The information summarized in this review came from two sources: a Medline search of all papers published in the literature and review of abstracts from recent scientific meetings. Since this is a rapidly changing field, the most recent information is published as abstracts and as such should be considered preliminary in nature. Moreover, some of the series contained only small number of patients or were published as a letter to editors. The findings of larger series should be considered more significant than smaller series.

The association between HGV and chronic hepatitis

is unclear. The prevalence of hepatitis G viremia was the same among blood donors with normal and elevated SGPT levels in both US and Australia studies.[2,21] The detection of HGV RNA in patients with various types of liver disease does not necessarily mean that HGV is the cause. Interpretation of current data is hampered by several factors. First, HGV can only be diagnosed using a PCR technique. Some of the differences in the prevalence of HGV among various groups might be the result of differences in PCR techniques or storage conditions of serum. PCR assay using primers from a highly conserved region such as sequences from the 5′ UTR is likely to be more sensitive than assays using primers from a less conserved region such as NS3.[26] Differences in primer sets and running condition can result in more than twofold differences in sensitivity (13.2 vs 5.3%).[19] Second, it is possible some of the observed differences of prevalence of HGV/GBV-C reported in the literature are the result of differences in the virulence of different isolates. Even though the prototype HGV and GBV-C are found to be different isolates of the same virus, there are differences in length and at the amino acid level. Heterogeneity in GBV-C genomic sequences has been reported.[15–18] Third, HGV commonly occurs as a coinfection with another hepatitis virus, usually HCV. This might be related to the common mode of transmission, such as transfusion. However, most existing data suggest that HGV coinfection does not alter the clinical course of chronic hepatitis B or C in these patients.

In studies that investigate the "natural history" of chronic HGV infection, such as prospective studies on transfusion associated hepatitis, there is a poor correlation between serum HGV RNA and the level of SGPT elevation.[44] The majority of patients do not develop chronic hepatitis.[25,41–43] Similarly, there is no relationship between HGV virological response and biochemical response to interferon therapy in patients coinfected with HGV/HCV.[53–55,81] These findings show that hepatitis G viremia frequently occurs in the setting without SGPT elevation, that is, biochemical evidence of hepatitis. Therefore, it is not clear that HGV is indeed a cause of chronic hepatitis. The finding of HGV/GBV-C RNA in serum of patients with fulminant hepatitis of unknown etiology (0[62–64] to 50%[61]) and cryptogenic cirrhosis (14[72] to 36%[74]) could be fortuitous. One of the most interesting findings of several groups is the unexplained high prevalence of HGV infection after liver transplantation, even though the HGV infection did not alter the clinical course in these patient or affect graft survival. Since the role of HGV as a etiologic agent of liver disease is unclear, therapy is not recommended at this point. Interferon could be used if HGV were to be demonstrated as a cause of liver disease. The development of a reliable serological assay should resolve some of these unanswered questions.

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