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Outbreak of Acute Hepatitis C Following the Use of Anti– Hepatitis C Virus—Screened Intravenous Immunoglobulin Therapy

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See editorial on page 1307.

Background & Aims: Hepatitis C virus (HCV) infection has been associated with intravenous (IV) immunoglobulin (Ig), and plasma donations used to prepare IV Ig are now screened to prevent transmission. Thirty-six patients from the United Kingdom received infusions from a batch of anti-HCV antibody-screened intravenous Ig (Gammagard; Baxter Healthcare Ltd., Thetford, Norfolk, England) that was associated with reports of acute hepatitis C outbreak in Europe. The aim of this study was to document the epidemiology of this outbreak. Methods: Forty-six patients from the United Kingdom treated with Gammagard (34 exposed and 12 unexposed to the batch) returned epidemiological questionnaires. Results: Eighty-two percent of the exposed patients (28 of 34) became positive for HCV RNA. Eighteen percent of the patients (6 of 34) who had infusions with this batch tested negative for HCV RNA, but 2 of the patients had abnormal liver function and subsequently seroconverted to anti-HCV antibody positive. Twenty-seven percent of the patients (9 of 34) developed jaundice, and 79% (27 of 34) had abnormal liver transferase levels. Virus isolates (n = 21), including an isolate from the implicated batch, were genotype 1a and virtually identical by sequence analysis of the NS5 region, consistent with transmission from a single source. Conclusions: Hepatitis C infection can be transmitted by anti-HCV-screened IV lg. Careful documentation of IV Ig batch numbers and regular biochemical monitoring is recommended for all IV Ig recipients.

Intravenous (IV) immunoglobulin (Ig) is an established therapy for immune deficiency. It is used in the management of primary¹ and secondary immune deficiency^{2,3} and as an immunomodulatory agent in many autoimmune diseases.⁴ As IV Ig therapy developed through the 1980s, outbreaks of non-A, non-B hepatitis were recognized with several different IV Ig products.⁵⁻¹⁰ Recent molecular analysis has confirmed hepatitis C virus (HCV) as the cause of these outbreaks.^{11,12} The development of efficient antibody tests for hepatitis C has now enabled the statutory introduction of screening and exclusion of anti-HCV antibody-positive plasma donors, although the acceptance of screening was controversial.¹³ There was concern that transmission of hepatitis C was still possible if plasma was donated by acutely infected individuals who had not yet seroconverted.^{14,15} Transmission could then occur if complete viral inactivation or removal did not take place during the manufacturing process. Therefore, although IV Ig preparations were thought to be safe and unlikely to transmit HCV infection, routine monitoring of liver function test results was recommended for all patients undergoing such therapy.¹⁶

Early in 1994, abnormal liver function test results were detected on routine testing among patients in the United Kingdom undergoing IV Ig therapy using the brand Gammagard (Baxter Healthcare Ltd., Thetford, Norfolk, England). At the same time, several cases of suspected acute hepatitis C infection were reported after the use of the same product in Sweden and Spain. In response, Gammagard was withdrawn worldwide on February 21, 1994. It became rapidly clear that in the United Kingdom and Spain, all patients developing possible HCV infection had been treated recently with one batch of the product. This enabled identification of all exposed patients. Other cases subsequently reported in the United States and in Sweden were associated with different contaminated batches of the product, and because several batches were implicated, identification and subsequent follow-up was more difficult.¹⁷ In this study, we report

Abbreviations used in this paper: CVID, common variable immunodeficiency; RT-PCR, reverse-transcription polymerase chain reaction. © 1996 by the American Gastroenterological Association 0016-5085/96/\$3.00

the initial follow-up of the exposed patients in the United Kingdom.

Patients and Methods

In late February 1994, abnormal liver function was detected in several patients in the United Kingdom who were receiving Gammagard. All of these patients had been treated with one particular batch (93F21AB11B) within the preceding 7 weeks (from December 20, 1993, to February 18, 1994). This batch was also associated with cases of acute hepatitis C in Spain. Data were obtained from the manufacturer detailing all centers in the United Kingdom supplied with Gammagard since 1991. Details of the batch numbers and the recall of all remaining stocks of Gammagard were used to identify and contact the centers where the implicated batch had been used. Thirty-six patients who had received injections from this batch from 19 local centers (care supervised from 9 regional immunology centers) were identified within the United Kingdom. We also identified 12 patients who underwent Gammagard therapy at these centers during the same period but who did not receive injections from this batch or any Gammagard lots released after 93F21AB11B. Their physicians were initially contacted by telephone and then invited to return a followup questionnaire. The questionnaire included center details, individual patient details (indication and history of IV Ig therapy, history of previous liver disease, details of current episode, and risk factors for HCV), and laboratory results. Any available laboratory data for the year before exposure were collected for each case. Abnormal liver function test results were defined as two times greater than baseline value for each individual. Data were analyzed using the World Health Organization epidemiology program EPI-INFO (version 5).

To confirm infection, clotted blood samples were obtained, and the serum was removed and frozen within 6 hours of venesection. HCV RNA was detected by reverse-transcription polymerase chain reaction (RT-PCR). Sera stored $(-20^{\circ}C)$ before exposure were available for 21 of 36 patients and were also tested for HCV RNA. Because RNA degrades easily, sera stored at the same time from a known case of long-standing HCV infection were used as positive control for 19 of 21 cases. To establish whether infection was caused by the same virus, the genotype and subtype of representative samples from several centers were ascertained. Analysis was performed on a segment (222 base pairs; positions 7975-8196) of the NS-5 gene, which was amplified, sequenced, and analyzed as previously described.¹⁸ Phylogenetic relationships were investigated between nucleotide sequences amplified from patients exposed to the implicated batch of Gammagard and epidemiologically unrelated type 1a variants from the United States and Europe (including United Kingdom, Ireland, and Europe) (Figure 1). Sequence distances were calculated using DNAML program (in PHYLIP inference package, version 3.5, University of Washington, Seattle, WA) in a dataset containing HCV-J (type 1b) as an outgroup. Control sequences were obtained from published sources. The analysis also included an NS-5 sequence recovered from the implicated batch of Gammagard.

Results

Patient Details

Forty-six questionnaires were returned from 48 identified patients who received Gammagard at the 19 local centers, regardless of the batch numbers within the last 14 months (from January 1993 to the withdrawal of Gammagard by Baxter Healthcare). Patient details are summarized in Table 1. No questionnaire was returned from the 2 remaining patients: a Greek child who received IV Ig while in intensive care before returning to Greece, and a woman with preexisting liver cirrhosis (HCV-related postblood products) who has since received a liver transplant. None of the 46 patients had a history of illicit intravenous drug use (street drugs), tattoos, or sexual contact with individuals with hepatitis. One patient who received injections from the implicated batch had a 2-year history of lichen planus (a condition suggested to be associated with HCV infection), but none of the rest had any history or evidence of other HCVrelated disorders such as membranous glomerulonephritis, cryoglobulinemia, or porphyria cutanea tarda. Two of the patients had worked within the health care field (one as a dentist and the other as a nurse).

Association With Batch Numbers of Gammagard and HCV Infection

To establish which batch was associated with the transmission of HCV in these cases in the United Kingdom, details of all batches of Gammagard received since January 1993 were available for 27 of 46 patients (14 HCV RNA-positive and 13 HCV RNA-negative). Univariate analysis was performed on each batch (n = 17) compared with HCV RNA detection (data not shown). Only 1 of 17 batches (93F21AB11B) was positively associated with transmission of HCV (χ^2 test, 17.1; P < 0.00003, Fisher's Exact Test). In all patients who returned the questionnaire (n = 46), the relative risk for being HCV RNA positive and having used the batch 93F21AB11B was 9.88 (Greenland-Robbins 95% confidence limits, 1.50 < relative risk < 64.92; P =0.0001) with an odds ratio of 51.33 (Cornfield 95% confidence limits, 4.84 < odds ratio < 1315).

HCV PCR

Twenty-eight of 34 patients (82.4%) treated with the batch (93F21AB11B) became HCV-positive as detected by PCR within 4 months of exposure. The remaining 6 exposed patients who have had documented infusions with batch 93F21AB11B have tested negative



Figure 1. Phylogenetic tree of HCV isolates from recipients compared with controls based on sequence analysis of the NS-5 region (see Patients and Methods). Controls were labeled by isolate and country of origin and recipients of Gammagard by isolate only.

Table 1. Patient Details

	Batch 93		
Clinical features	Exposed	Not exposed	Total
No. of patients	34	12	46
Age (yr, mean [range])	42.8 (6-77)	37.8 (23-52)	41.5
Male/female	15/19	7/5	22/24
Indication for IV Ig therapy			
CVID	18	10	28
Ig subclass deficiency	8	1	9
Chronic lymphocytic leukemia	3		3
Myeloma	2		2
X-linked gammaglobulinemia	1		1
Drug-induced hypogammaglobulinemia	1		1
Hypogammaglobulinemia due to intestinal lymphangiectasia	1		1
X-linked hyper IgM syndrome		1	1

for HCV using PCR; 4 patients were tested on at least three occasions up to 4 months after exposure, and the other 2 have been tested twice. Two of the HCV RNAnegative patients had abnormal liver function test results and have seroconverted for anti-HCV. The first patient had myeloma and recommenced IV Ig therapy with another anti-HCV-screened product. The other had Ig deficiency and Crohn's disease and developed abnormal liver function after exposure (documented by his primary care physician); however, when finally tested for HCV markers (101 days after exposure), he had seroconverted for anti-HCV antibody but RNA was negative. In HCVpositive cases by PCR, 26 of 28 patients (92.3%) tested positive on the first test after exposure. The mean length of time from exposure to batch 93F21AB11B to the first positive HCV PCR test result was 37.5 days (range, 7-71 days; n = 22; 1 SD = 19.3). Nine of the 12 patients who underwent Gammagard therapy but who did not receive the implicated batch (93F21AB11B) have all tested negative for HCV PCR on at least two occasions. Of the 3 remaining patients, 1 patient was positive by PCR previously and had chronic hepatitis C infection after transmission by previous IV Ig product (not Gammagard); 1 patient has been tested only once (negative); and data were not available for the third patient. In 21 of the 34 exposed patients (61.8%), sera were available before exposure (in 15 of 21 patients [71.4%] sera were available from the month immediately before their exposure) and they tested for RT-PCR. Only 1 of these patient was HCV RNA-positive before exposure. He was a patient with common variable immunodeficiency (CVID) and autoimmune hemolytic anemia who had received other blood products in the past. Genotyping of 20 isolates from 14 patients have all shown genotype 1a.

Further sequence analysis of the NS5 region of the

viral isolates has shown no significant nucleotide variation between virus isolates from separate cases or the sequence amplified from batch 93F21AB11B (Figure 1). This is consistent with transmission from this batch and contamination from a single donor.

HCV Serology

Only 22 of the 34 (65%) exposed patients had been tested for anti-HCV antibody by second-generation enzyme-linked immunosorbent assay. Three were positive (2 CVID and 1 Ig subclass deficiency) on initial testing 1-3 months after exposure. Seventeen of the patients who initially tested negative have been tested a second time and 6 patients had seroconverted (3 CVIDs, 1 Ig subclass deficiency, and 2 myelomas).

Clinical Features

Nine of the 34 exposed patients (27%) developed jaundice (bilirubin level, >50 IU/L), and 27 of the 34 (79.4%) had abnormal liver transferase levels (aspartate aminotransferase or alanine aminotransferase) within 4 months after the first exposure to the contaminated batch. In all patients with abnormal liver transaminase levels, abnormal values were found on more than one occasion. The mean time from individual exposure to batch 93F21AB11B to the first documented abnormal liver transaminase level was 44.59 days (range, 4-119 days; n = 22; with 60% of values abnormal on the first available testing after exposure). Eighteen of the 34 patients who received the contaminated batch (52.9%) developed the following symptoms: malaise in 13, dark urine in 3, pruritus in 2, and food intolerance or nausea in 4. Histological analysis of the liver was performed on 3 patients: 2 had acute inflammation of the liver typical of HCV hepatitis. The third was a patient with chronic lymphocytic leukemia who died suddenly of unrelated causes; postmortem examination showed marked lymphocytic infiltration of the liver with lymphoid follicle formation. Immunohistochemical staining has shown the cells to be predominately of T-cell origin (suggesting HCV rather than chronic lymphocytic leukemia as the cause of the changes). Only 1 of the 12 patients not exposed to the implicated batch (93F21AB11B) had any documented change in liver function test results; this change was transient after a chest infection treated with broad-spectrum antibiotics.

The 4 patients exposed to the batch but who had no findings of HCV viremia or anti-HCV seroconversion did not seem to be significantly different in age, sex, indication for IV Ig (two CVIDs and two Ig subclass deficiencies), or dose of the implicated batch.

In summary, of 34 patients in the United Kingdom

Country	Year	Study	Product	Outbreak	HCV PCR	Cirrhosis
United Kingdom	1983	Lane, ⁶ Lever et al. ⁷	British Blood Products Laboratory, Elstree	12/12 IV lg-treated patients developed non-A, non-B hepatitis	5/5 positive	3 cases by 1986
United States	1988	Ochs et al.⁵	Hyland Therapeutics Division, California	7/16 IV Ig-treated patients developed non-A, non-B hepatitis	10/15 positive	2 cases by 1986
Sweden	1988	Bjorkander et al. ⁸	Gammonativ, Kabivitrium	16/77 treated patients developed non-A, non-B hepatitis	8/10 positive	3 cases in initial report
Scotland	1989	Williams et al. ⁹	Scottish National Blood Transfusion Service	4/34 treated patients developed non-A, non-B hepatitis	3/4 positive	Not known
Sweden	1986	Weiland et al. ¹⁰	Gammonative, Kabivitrium	4 patients with non-A, non-B hepatitis	Not known	2 cases in initial report
Sweden	1986	Hammarstrom and Smith ³¹	Not reported	1 patient with non-A, non-B hepatitis	1/1 positive	1 in initial report
Norway/ Sweden	1994	Bjoro et al. ¹²	Gammonativ, Kabivitrium	17 HCV-positive by PCR from 54 patients treated 1982– 1986	17/54 positive	5 cases by 1994
United Kingdom	1994	Healey (present study)	Gammagard; Baxter– Hyland	28 HCV-positive by PCR from 36 patients exposed to one batch of IV	28/34 positive	Not known
United States	1994	MMWR ¹⁷	Gammagard; Baxter– Hyland	110 suspected cases of HCV infection treated with Gammagard	Not known	Not known

Table 2. Summary of Previous Outbreaks of HCV in Patients Undergoing IV Ig Therapy

followed up since exposure to a contaminated batch (93F21AB11B) of Gammagard, 30 developed HCV infection. Twenty-eight were found to be HCV positive by PCR, and 2 patients were anti-HCV positive with abnormal liver function tests. Sequence analysis has shown almost identical virus isolates from the implicated batch as well as all 20 isolates tested from the recipients.

Discussion

We have shown that the use of an IV Ig product (Gammagard) made from blood screened for anti-HCV antibody was associated with the transmission of acute hepatitis C from one contaminated batch. No infection was found in patients treated with 16 different batches of the same product in the United Kingdom during the 14 months before withdrawal. Analysis of virus isolates from the infected patients has shown the same subtype of the virus, and nucleotide sequence analysis of the NS5 region of the viral genome shows virtually no variation between any of the isolates. An identical sequence has also been amplified from the implicated batch. Such findings are consistent with infection from a single donor.

For breakthrough of HCV infection to have occurred, there must have been both failure of anti-HCV screening to detect donor infection and lack of complete removal of infectious HCV by the production method. Anti-HCV screening can fail if plasma is donated after exposure to HCV but before seroconversion or if plasma is donated by infected individuals who remain seronegative for a long term.¹⁹ Each batch of Gammagard is produced from a plasma pool (approximately 12,000 L) made from approximately 15,000 individual donations from several thousand donors. The plasma pool then undergoes cryoprecipitation and alcohol precipitation to produce several protein fractions; the γ -globulin-containing fraction is further purified by chromatography. Although the alcohol precipitation steps have been shown to denature retroviruses, the ability to remove HCV is unproven.²⁰ HCV RNA could still be detected by nested PCR in the γ -globulin fraction but at a greatly reduced titer compared with that of the starting plasma pool, so that infectivity was thought to be unlikely.¹⁵ In addition, IV Ig made from infectious plasma using various methods, including that used to produce Gammagard, had been shown not to transmit HCV to chimpanzees in limited animal tests.²¹ Whether this outbreak is related to HCV screening or proves to be restricted to the manufacturing process (now modified by the addition of solvent or detergent inactivation) is unknown.

Because of the concern for potential HCV transmission, improvements in the production of IV Ig have been introduced, such as the addition of a solvent detergent step for the inactivation of HCV because this virus is sensitive to organic solvents. Further improvements of antibody-based screening would not completely remove the risk of seronegative but HCV RNA-positive donations. The adoption of HCV RNA detection from individual donations by RT-PCR would be expensive and difficult to standardize. The readoption of surrogate markers such as abnormal transaminase values may further identify HCV-positive donors who remain negative on anti-HCV tests. However, HCV infection is often found with persistently normal liver function despite active liver disease.²² One possible option would be introducing HCV RNA testing of the finished IV Ig product, although interpretation of positive results remains uncertain with regard to infectivity.

In immunocompetent individuals, hepatitis C usually causes chronic infection that may progress to cirrhosis and hepatocellular carcinoma.²³⁻²⁶ There have been several previous outbreaks of non-A, non-B hepatitis associated with the use of IV Ig (now known to be caused by HCV).^{5-8,10,23-26} Many of the patients developed significant liver disease (Table 2),^{8,12,27} and cirrhosis was found in 17 of 61 patients (27.9%). Thus, in this patient group, more severe and rapid progression was found than in immunocompetent individuals. Although this may reflect bias in ascertaining and reporting of more severe outcomes, these complications have occurred during a relatively short period (<10 years) and therefore could still underestimate their long-term liver-related morbidity. The only accepted therapy for HCV infection is interferon alfa, although its use is limited, even in immunocompetent individuals, because of poor efficacy, high relapse rates, and significant side effects.²⁸ The use of interferon alfa to treat HCV infection in immune deficiency has been shown to improve liver biochemistry.^{8,12,27,29} However, long-term success in curing HCV infection in patients with primary immunodeficiency has only been suggested in 1 of 16 reported cases. Because interferon alfa therapy has been associated with higher rates of long-term clearance when used in the acute stages,³⁰ treatment should be offered as soon as infection is confirmed. This may improve the chance of eradicating HCV and is the subject of further study in the followup of these patients.

The high rate of HCV antibody seroconversion in this group of antibody-deficient patients is somewhat surprising. However, the range of severity of antibody failure is reflected in the immunodeficiency diseases for which the IV Ig therapy was used. Patients with chronic lymphocytic leukemia, myeloma, and selective antibody deficiency make antibodies to some antigens (but often only to those proteins in nature,^{2,3,16}; consequently, seroconversion to HCV is not unexpected. However, antibodies do not usually develop in patients with CVID; if they do, the antibodies may be transient. These data suggest that it is worth checking regularly for anti-HCV antibody in all such patients because even transient evidence of such antibodies may be the only indication of HCV transmission.

The transmission of viruses through the use of blood and blood products has been a major medical problem, perhaps most tragically illustrated with the inadvertent human immunodeficiency virus infection of hemophiliacs. However, the problem has not been restricted to human immunodeficiency virus, as clearly shown by the current outbreak of hepatitis C that accompanied the use of screened IV Ig (Gammagard). This emphasizes the importance of regarding Ig preparations with the same care that is afforded to other blood products. Careful documentation of batch numbers and regular biochemical monitoring is recommended for all IV Ig recipients.

References

- Chapel HM. Consensus in diagnosis and management of primary antibody deficiencies. BMJ 1994;308:581–585.
- Chapel HM, Lee M, Hargreaves R, Pamphilon DH, Prentice AG. Randomized trial of intravenous immunoglobulin as prophylaxis against infection in plateau-phase multiple myeloma. The UK Group for Immunoglobulin Replacement Therapy in Multiple Myeloma. Lancet 1994;343:1059–1063.
- Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukemia. Intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukemia. A randomized, controlled clinical trial. N Engl J Med 1988;319:902–907.
- Dwyer JM. Manipulating the immune system with immune globulin. N Engl J Med 1992;326:107–116.
- Ochs HD, Fischer SH, Virant FS, Lee ML, Kingdon HS, Wedgwood RJ. Non-A, non-B hepatitis and intravenous immunoglobulin. Lancet 1985; 1:404–405.
- Lane RS. Non-A, non-B hepatitis from intravenous immunoglobulin (letter). Lancet 1983;2:974–975.
- Lever AM, Webster AD, Brown D, Thomas HC. Non-A, non-B hepatitis occurring in agammaglobulinaemic patients after intravenous immunoglobulin. Lancet 1984;2:1062–1064.
- Bjorkander J, Cunningham RC, Lundin P, Olsson R, Soderstrom R, Hanson LA. Intravenous immunoglobulin prophylaxis causing liver damage in 16 of 77 patients with hypogammaglobulinemia or IgG subclass deficiency. Am J Med 1988;84:107–111.
- Williams PE, Yap PL, Gillon J, Crawford RJ, Urbaniak SJ, Galea G. Transmission of non-A, non-B hepatitis by pH4-treated intravenous immunoglobulin (see comments). Vox Sang 1989;57:15– 18.
- Weiland O, Mattsson L, Glaumann H. Non-A, non-B hepatitis after intravenous gammaglobulin (letter). Lancet 1986;1:976–977.
- Yap PL, McOmish F, Webster DB, Hammarstrom L, Edward Smith Cl, Bjorkander J, Ochs HD, Fischer SH, Quinti I, Simmonds P. Hepatitis C virus transmission by intravenous immunoglobulin. J Hepatol 1994;21:455–460.
- Bjoro MD, Froland SS, Yun Z, Samdal HH, Haaland MD. Hepatitis C infection in patients with primary hypogammaglobulinemia after treatment with contaminated immune globulin. N Engl J Med 1994; 331:1607–1611.
- Finlayson JS, Tankersley DL. Anti-HCV screening and plasma fractionation: the case against. Lancet 1990;335:1274–1275.
- Lefrere JJ, Mariotti M, Trepo C, Li JS, Lunel F, Frangeul L, Letourneur F, Laporte JP, Jullien AM. Testing for HCV-RNA in commercial intravenous immunoglobulins (letter; comment). Lancet 1993; 341:834–834.
- 15. Yei S, Yu MW, Tankersley DL. Partitioning of hepatitis C virus

during Cohn–Oncley fractionation of plasma. Transfusion 1992; 32:824–828.

- 16. Spickett GP, Misbah SA, Chapel HM. Primary antibody deficiency in adults. Lancet 1991;337:281–284.
- Meeks EL, Beach MJ. Outbreak of hepatitis C associated with intravenous immunoglobulin administration—United States, October 1993–June 1994. Morb Mortal Wkly Rep 1994;43:505– 509.
- Simmonds P, McOmish F, Yap PL, Chan SW, Lin CK, Dusheiko G, Saeed AA, Holmes EC. Sequence variability in the 5' noncoding region of hepatitis C virus: identification of a new virus type and restrictions on sequence diversity. J Gen Virol 1993; 74:661–668.
- 19. Alter M. The detection, transmission and outcome of hepatitis C infection. Infect Agents Dis 1993;2:155–166.
- Mitra G, Wong MF, Mozen MM, McDougal JS, Levy JA. Elimination of infectious retroviruses during preparation of immunoglobulins. Transfusion 1986;26:394–397.
- Biswas RM, Nedjar S, Wilson LT, Mitchell FD, Snoy PJ, Finlayson JS, Tankersley DL. The effect on the safety of intravenous immunoglobulin of testing plasma for antibody to hepatitis C. Transfusion 1994;34:100–104.
- Healey CJ, Chapman RWG, Fleming KA. Liver histology in hepatitis C infection: a comparison between patients with persistently normal or abnormal transaminases. Gut 1995;37:274–278.
- Alter MJ, Margolis HS, Krawczynski K, Judson FN, Mares A, Alexander WJ, Hu PY, Miller JK, Gerber MA, Sampliner RE, et al. The natural history of community-acquired hepatitis C in the United States. The Sentinel Counties Chronic non-A, non-B Hepatitis Study Team (see comments). N Engl J Med 1992;327:1899– 1905.
- 24. Esteban JI, Lopez TJ, Genesca J, Madoz P, Viladomiu L, Muniz E, Martin VC, Rosell M, Allende H, Vidal X, et al. High rate of

infectivity and liver disease in blood donors with antibodies to hepatitis C virus (see comments). Ann Intern Med 1991; 115:443-449.

- Tremolada F, Casarin C, Alberti A, Drago C, Tagger A, Ribero ML, Realdi G. Long-term follow-up of non-A, non-B (type C) posttransfusion hepatitis. J Hepatol 1992;16:273–281.
- Yano M, Yatsuhashi H, Inoue O, Inokuchi K, Koga M. Epidemiology and long-term prognosis of hepatitis C virus infection in Japan. Gut 1993;34(Suppl):S13–S16.
- 27. Thomson BJ, Doran M, Lever AM, Webster AD. Alpha-interferon therapy for non-A, non-B hepatitis transmitted by gammaglobulin replacement therapy. Lancet 1987;1:539–541.
- Tine F, Magrin S, Craxi A, Pagliaro L. Interferon for non-A, non-B chronic hepatitis. A meta-analysis of randomised clinical trials. J Hepatol 1991;13:192–199.
- Lockner D, Bratt G, Lindborg A, Tornebohm E. Acute unidentified hepatitis in a hypogammaglobulinaemic patient on intravenous gammaglobulin successfully treated with interferon. Acta Med Scand 1987;221:413–415.
- Lampertico P, Rumi M, Romeo R, Craxi A, Soffredini R, Biassoni D, Colombo M. A multicenter randomized controlled trial of recombinant interferon-alpha in patients with acute transfusionassociated hepatitis C. Hepatology 1994;19:19–22.
- Hammarstrom L, Smith CI. IgM production in hypogammaglobulinaemic patients during non-A, non-B hepatitis (letter). Lancet 1986;1:743.

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