LIT.001.0851

The New England
Journal of Medicine

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Volume 325 NOVEMBER 7, 1991 Number 19

HEPATITIS C VIRUS INFECTION IN POST-TRANSFUSION HEPATITIS

An Analysis with First- and Second-Generation Assays

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Abstract *Background.* The causes of post-transfusion non-A, non-B hepatitis are still not fully defined, nor is it clear how accurate the tests are that are used to screen blood donors for hepatitis C virus (HCV) and to diagnose post-transfusion hepatitis caused by infected blood.

Methods. We used two first-generation enzyme-linked immunoassays (EIAs) and one second-generation immunoassay to test for anti-HCV antibodies in serum samples collected between 1976 and 1979 in the Transfusion-Transmitted Viruses Study (from 1247 patients who underwent transfusion and 1235 matched control subjects who did not receive transfusions). We tested serum collected before and after infection from the patients in whom non-A, non-B hepatitis developed, serum from their blood donors, and serum from 41 of the control subjects who had hepatitis unrelated to transfusion.

Results. Of the 115 patients in whom post-transfusion non-A, non-B hepatitis developed, the initial serum samples of 111 were anti-HCV–negative; after hepatitis developed in these 111 patients, the first-generation EIAs detected anti-HCV in 51 (46 percent), and the second-generation assay detected anti-HCV in an additional 16 (14 percent), for a total of 60 percent. Of 40 controls, 37 were anti-HCV–negative initially, and none seroconverted after hepatitis developed. If the 3 percent rate of non-A, non-B, non-C hepatitis among the controls (37 of 1235) was applied to the 1247 transfusion recipients, only 74 of the 111 cases of hepatitis were attributable to the transfusion. Thus, 91 percent (67 of 74) of the cases of post-tranfusion hepatitis were caused by HCV. Of the 99 donors, 60 were HCV-positive (9 on second-generation tests only) and 39 were not.

Conclusions. Nearly all cases of non-A, non-B post-transfusion hepatitis are caused by HCV. Screening with a second-generation assay improves the rate of detection of HCV infection in patients with post-transfusion hepatitis and in blood donors. The use of this test showed a 3.6 percent risk of non-A, non-B, non-C hepatitis, which was not significantly different from the rate in the controls (3.0 percent). (N Engl J Med 1991;325:1325-9.)

ALTHOUGH non-A, non-B hepatitis was first recognized in 1974,[1,2] identification of the responsible etiologic agent or agents proved difficult. Prospective studies conducted in the United States during the 1970s demonstrated that hepatitis developed as a complication in 5 to 12 percent of the recipients of blood from volunteer donors, with approximately 90 percent of the cases diagnosed as non-A, non-B hepatitis.[3-6] It is believed that the incidence of non-A, non-B post-transfusion hepatitis has decreased since the implementation in 1986 of donor screening for surrogate markers — i.e., an elevated serum level of alanine aminotransferase activity or the presence of antibody to hepatitis B core antigen (anti-HBc), which are associated with an increased risk of transmitting non-A, non-B hepatitis.[7-11]

In 1989 Choo et al. reported the cloning of a part of the hepatitis C virus (HCV) genome isolated from experimentally infected chimpanzee plasma.[12] Specificity for parenterally transmitted non-A, non-B hepatitis was quickly confirmed.[13,14] HCV is a major cause of transfusion-associated non-A, non-B hepatitis. In mid-1990, routine screening of all donors with first-generation assays to detect antibody to a nonstructural antigen of HCV was adopted in the United States. However, not all donors who transmit HCV are anti-HCV–positive, and not all persons with non-A, non-B hepatitis seroconvert according to these assays.[15,16] Second-generation assays, which include polypeptides that are additional gene products (core and putative-protease epitopes), are now being evaluated.

In this report, we compare the recognition of anti-HCV by first- and second-generation enzyme-linked immunoassays (EIAs) among transfusion recipients in

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Supported by a contract (NO1-HB-42972) with the National Heart, Lung, and Blood Institute.

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whom non-A, non-B hepatitis developed and among their blood donors. We also compare the serologic and clinical characteristics of hepatitis in the transfusion recipients with those in control subjects with non-A, non-B hepatitis who did not receive transfusions. In addition, we examine the association of non-A, non-B hepatitis among the transfusion recipients with the presence of anti-HCV and surrogate markers in their donors' serum. Data from transfusion recipients, their donors, and hospitalized control subjects enrolled in the Transfusion-Transmitted Viruses Study served as the basis for these evaluations.

Methods

Recruitment of Study Subjects

The Transfusion-Transmitted Viruses Study was conducted at medical centers in New York, St. Louis, Los Angeles, and Houston. Patients who received transfusions and hospitalized control subjects who did not were enrolled in a pilot phase in 1974–1975 and in the main study from 1976 to 1979. Criteria for enlistment and follow-up have been described in detail.[7-9] To be included in this analysis, study subjects had to complete at least 148 days of follow-up.

Evaluation for Hepatitis

Hepatitis was diagnosed if between 11 and 180 days after transfusion (or after enrollment for the controls), the level of alanine aminotransferase was abnormal (≥45 IU per liter) in at least two consecutive blood specimens drawn within a period of 3 to 17 days, with the level in at least one specimen ≥90 IU per liter. Non-A, non-B hepatitis was diagnosed if there was no indication of liver disease of nonviral origin and no serologic evidence of newly acquired hepatitis A or hepatitis B virus (HBV) infection. Each case was reviewed by study investigators and by a committee of independent experts whose members had no knowledge of whether the patient had received a transfusion. Study subjects were classified as having non-A, non-B hepatitis only if both groups were in agreement. The hepatitis was classified as chronic if the alanine aminotransferase level remained elevated for at least six months. Cases in which the alanine aminotransferase level returned to normal were considered to involve acute hepatitis that resolved. Subjects followed for less than six months who still had an elevated alanine aminotransferase level when last seen were classified as having non-A, non-B hepatitis with an indeterminate outcome.

Previous Laboratory Procedures

Each serum specimen from the transfusion recipients and controls was tested for hepatitis B surface antigen (HBsAg), antibody to HBsAg (anti-HBs), and anti-HBc by radioimmunoassay (Abbott Laboratories, North Chicago). HBsAg testing of donor serum was by radioimmunoassay or reverse passive hemagglutination. Selected serum samples were tested for antibody to hepatitis A virus (Abbott Laboratories) if the recipient had any evidence of hepatitis. At each study center, samples from the donors and recipients were analyzed for alanine aminotransferase activity by an automated kinetic spectrophotometric assay at 37°C with a standardized procedure, identical instruments, and centralized quality control. The upper limit of normal was defined as <45 IU per liter, which is 2 SD above the mean of logarithmically transformed values.

Current Study Population

The participants in the present study were 115 patients with non-A, non-B hepatitis among the 1247 transfusion recipients in the main phase of the Transfusion-Transmitted Viruses Study and the 41 subjects with non-A, non-B hepatitis among the 1235 controls who did not receive transfusions. Specimens adequate for the evaluation of seroconversion were available for all 115 transfusion recipients and for 40 of the 41 controls. The samples we tested were those drawn at enrollment (i.e., before transfusion, for the recipients), at the time of onset of hepatitis, 3 and 6 months after enlistment, and when the participants were last evaluated, 10 or more months after entry into the study. Eleven transfusion recipients and one control subject with HBV, as well as four recipients and three controls whose initial blood specimens were found to be anti-HCV–positive, were excluded from analysis. The present study is thus based on 111 patients with non-A, non-B hepatitis among 1232 recipients of blood transfusions and 37 persons with non-A, non-B hepatitis among 1230 controls. Specimens from every donor were available for 99 of the 111 transfusion recipients with non-A, non-B hepatitis.

Laboratory Procedures

Donor, recipient, and control serum samples collected during the main phase of the study were retrieved from storage and tested in duplicate for anti-HCV by three different assay methods in two independent laboratories. The assays included two first-generation EIAs (ELISA, Ortho Diagnostic Systems, Raritan, N.J.; and EIA, Abbott Laboratories), both of which detect antibody to a single gene product, C100-3 antigen, a nonstructural component of HCV; and a second-generation EIA that detects antibodies to a putative protease (33C) and the core region (pHCV-34) of HCV, as well as the C100-3 antigen (Abbott Laboratories). The samples were randomized and coded so that the laboratories could not distinguish their source.

All positive specimens were retested in duplicate. Repeatedly reactive specimens were tested by supplemental assays for validation. For assays validating the Abbott first-generation test,[17] synthetic peptides sp42, sp117, and sp65 from the C100-3 region were used as antigens. Samples that were nonreactive for these peptides were tested in a solution-blocking or inhibition assay,[17] with recombinant antigen expressed in *Escherichia coli* as a chimeric CKS protein containing 256 of the 363 amino acids from the C100-3 region of HCV. Samples repeatedly reactive on either first- or second-generation assays were further tested with the use of synthetic peptides from the C100-3 (sp65, sp67) and core (sp75) regions, as well as recombinant antigen (pHCV-38) expressed in *E. coli* as a chimeric CKS protein from the protease (33C) region of HCV. Only repeatedly reactive specimens that were also reactive in one or more validation assays were considered positive. All serum confirmed to be reactive by the first-generation assay was also confirmed to be reactive by the second-generation assay.

For statistical comparisons, all continuous variables were treated as categorical variables, as defined in the tables. Analyses used the two-tailed chi-square or Fisher's exact test.

Results

The rates of anti-HCV seroconversion among the transfusion recipients and control subjects with non-A, non-B hepatitis are shown in Table 1. Among the 111 transfusion recipients with non-A, non-B hepatitis who were initially anti-HCV–negative, seroconversion was detected in 51 (46 percent) by the first-generation assay. In an additional 16 patients with seroconversion (14 percent), it was detected only by the second-generation assay. Seroconversion was not detected in any control subjects by either test ($P<0.0001$).

The recipients of blood transfusions who seroconverted to anti-HCV generally had more severe disease and higher peak alanine aminotransferase values (≥450 IU per liter) than either the transfusion recipients who did not seroconvert or the control subjects (Table 2), and they had a higher incidence of chronic hepatitis ($P<0.0001$). Correspondingly, symptoms ($P<0.005$) and jaundice ($P\leq0.0001$) were significant-

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Table 1. Anti-HCV Seroconversion According to First- and Second-Generation Assays in Transfusion Recipients and Controls with Non-A, Non-B Hepatitis.

Group	No. Susceptible	Anti-HCV Seroconversion		
		1st- and 2nd-generation assays*	2nd-generation assay only	Total
		number (percent)		
Controls	37	0	0	0
Transfusion recipients	111	51 (46)	16 (14)	67 (60)

*All positive results on first-generation assay were also positive on second-generation assay.

ly more frequent among anti-HCV–positive transfusion recipients with non-A, non-B hepatitis than among anti-HCV–negative subjects with hepatitis. Except for the interval from transfusion to the first detected increase in alanine aminotransferase activity, the clinical features of the cases of hepatitis detected only by the second-generation assay did not differ significantly from those of the cases detected by the first-generation test ($P>0.10$). The interval to the first increase in alanine aminotransferase was longer than six weeks in 11 of the 16 patients (69 percent) with post-transfusion hepatitis detected only by the second-generation assay, as compared with 35 percent of those whose serum was positive according to both assays ($P<0.02$). The clinical features of hepatitis in the anti-HCV–negative transfusion recipients were not significantly different from those in the control subjects.

The relation between anti-HCV positivity in the donor and anti-HCV seroconversion in the recipient could be determined in 99 transfusion recipients for whom all donors were tested (Table 3). Only 4 (10 percent) of 39 patients given blood that was negative for anti-HCV according to both assay systems became anti-HCV–positive; two of the four seroconversions were detected only by the second-generation assay. In contrast, of 60 transfusion recipients with hepatitis who were given blood that was anti-HCV–positive on first- or second-generation tests, 43 (72 percent) seroconverted according to both assays, and in another 12 recipients (20 percent) seroconversion was detected only by a second-generation assay, for an overall detection rate of 92 percent. Nine patients received blood that was anti-HCV–positive only according to the second-generation test. Of these, seven seroconverted, and four of the conversions were recognized only by the second-generation assay.

Table 4 analyzes the relation between anti-HCV seroconversion in the 99 transfusion recipients with non-A, non-B hepatitis and the presence of anti-HCV or surrogate markers in the blood they were given. A total of 55 patients received one or more units of blood that was positive for surrogate markers. Of these, 45 (82 percent) received blood that was also anti-HCV–positive in the same unit. Among those who received units that contained anti-HCV, the seroconversion rate was not influenced by the presence (91 percent) or absence (93 percent) of surrogate markers in the same unit. None of the eight patients who had post-transfusion hepatitis after receiving blood positive only for surrogate markers had seroconversion to anti-HCV. Surrogate markers were absent from the units given to the four patients who seroconverted after the transfusion of anti-HCV–negative blood.

Discussion

In this study, serologic evidence of HCV infection was detected by first- and second-generation assays in 60 percent of the patients with post-transfusion non-A, non-B hepatitis. This rate is lower than that reported by others using only first-generation assays. Alter and coworkers at the National Institutes of Health identified HCV infection in all 15 transfusion recipients with chronic hepatitis, and in 3 of 5 patients in whom the hepatitis resolved.[15] Their analysis used more stringent criteria for the diagnosis of hepatitis than the analysis of our group. They required two alanine aminotransferase values at least twice the upper limit of normal, with one exceeding 2.5 times normal. Using the National Institutes of Health criteria,

Table 2. Clinical Characteristics of Non-A, Non-B Hepatitis in Transfusion Recipients and Controls, According to Anti-HCV Seroconversion Status.*

Characteristic	Controls (N = 37)	Transfusion Recipients		
		No seroconversion (N = 44)	Seroconversion on 1st- and 2nd-generation assays (N = 51)	Seroconversion on 2nd-generation assay only (N = 16)
Chronicity — no. of patients (%)				
Resolved	31 (84)	37 (84)	19 (37)	6 (38)
Chronic	2 (5)	4 (9)	27 (53)	7 (44)
Indeterminate	4 (11)	3 (7)	5 (10)	3 (19)
First increase in ALT				
At ≥6 wk — no. of patients (%)	14 (38)	24 (55)	18 (35)	11 (69)
Median no. of days	28	50	39	51
Peak ALT				
≥450 IU/liter — no. of patients (%)	6 (16)	3 (7)	35 (69)	8 (50)
Median level — IU/liter	144	156	604	466
Symptoms and jaundice — no. of patients/no. with data available (%)				
Symptoms	6/29 (21)	5/41 (12)	17/44 (39)	5/15 (33)
Jaundice	0/29	0/41	11/45 (24)	3/15 (20)
Either or both	6/29 (21)	5/41 (12)	19/45 (42)	6/15 (40)

*Because of rounding, percentages do not always total 100. ALT denotes alanine aminotransferase.

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Table 3. Donor Anti-HCV Status and Seroconversion in Transfusion Recipients with Non-A, Non-B Hepatitis.*

Donor Anti-HCV Status	Transfusion Recipients		
	No seroconversion (N = 40)	Seroconversion on 1st- and 2nd-generation assays (N = 45)	Seroconversion on 2nd-generation assay only (N = 14)
	no. of patients (%)		
Negative on all assays	35 (90)	2 (5)	2 (5)
Positive on any assay			
Total	5 (8)	43 (72)	12 (20)
First and second generation	3 (6)	40 (78)†	8 (16)†
Second generation only	2 (22)	3 (33)†	4 (44)‡

*For 12 transfusion recipients with non-A, non-B hepatitis, the donors were not tested for all markers; these 12 are not included here.

†P = 0.015 by Fisher's exact test.

‡P = 0.05 by Fisher's exact test.

Esteban and his colleagues detected anti-HCV seroconversion in 89 percent of 27 cases of non-A, non-B post-transfusion hepatitis.[18] The cases of chronic hepatitis selected for evaluation by Alter et al. were of several years' duration, and many had biopsy evidence of chronic hepatitis or cirrhosis. Some of these cases were also proved to be infectious through experimental studies in chimpanzees. In contrast, the patients with post-transfusion hepatitis in our study were tested without selection for chronicity or infectivity.

Our simultaneous study of a control group that did not undergo transfusion makes it possible to use another approach to determine the proportion of cases of non-A, non-B post-transfusion hepatitis caused by HCV. From populations of almost identical size in the Transfusion-Transmitted Viruses Study, there were 111 cases of hepatitis among the transfusion recipients, of which 67 were due to HCV, and 37 cases of hepatitis among the controls, none of which were due to HCV. Assuming that the transfusion recipients had the same proportion of cases of hepatitis unrelated to transfusion as the controls, 74 of the 111 cases would be attributable to blood transfusion. Of the 74, 67 had demonstrable anti-HCV seroconversion — a rate of 91 percent, which is in accord with other studies.

Comparison with the controls in the Transfusion-Transmitted Viruses Study can also be used to estimate the residual incidence of hepatitis not identified in this study as due to HCV. Among the transfusion recipients, the overall incidence of non-A, non-B hepatitis was 9 percent (111 of 1232), with an incidence of HCV of 5.4 percent (67 of 1232). The residual incidence among the transfusion recipients of non-A, non-B hepatitis not due to HCV was thus 3.6 percent, which is not significantly different from the rate of hepatitis observed among the control subjects (37 of 1230, or 3.0 percent; P = 0.25). This observation suggests the possibility that HCV accounts for the vast majority, if not all, of the non-A, non-B hepatitis transmitted by blood transfusion.

There are several possible explanations for the cases of hepatitis seen in recipients and in controls that were not associated with anti-HCV seroconversion. These cases may have been due to HCV infection with an immunologic response not detected by the assays used, or to an agent other than HCV. Infection with another agent, however, implies a rate of nosocomial infection that seems surprisingly high. Reactivation of a latent infection by hospitalization or surgery is another possibility. If these cases had a viral cause, however, they appeared to be relatively innocuous, as compared with the disease seen in transfusion recipients with HCV. Finally, they may have resulted from one or more noninfectious etiologic factors that are associated with hospitalization but unrelated to transfusion. Regardless, the clinical similarities between the control subjects and the transfusion recipients who did not seroconvert suggest that they may have had disease of similar origins.

The second-generation assay detected anti-HCV among an additional 14 percent of the transfusion recipients with non-A, non-B hepatitis, for a 31 percent increase over the number of HCV-related cases identified by the first-generation assay. This increase could be due to the core and protease epitopes included in the second-generation assay and in some cases to an earlier response to these epitopes than to the C100-3 nonstructural antigen.

Testing the donors of the blood received by those with post-transfusion hepatitis allowed us to assess the effectiveness of surrogate markers and first-generation anti-HCV assays in donor screening. Among the cases of HCV identified in this study, 73 percent (43 of 59) were associated with the presence of surrogate markers in the donors, a rate similar to that predicted before HCV was identified.[9,10] The use of surrogate markers in the United States since 1986 therefore appears to be well justified.

The first-generation assay detected one or more units of blood from anti-HCV–positive donors administered to 81 percent of the patients who seroconverted and for whom all donor units were tested. The use of

Table 4. Anti-HCV Seroconversion in Transfusion Recipients with Non-A, Non-B Hepatitis in Relation to the Anti-HCV and Surrogate-Marker Status of the Donors.

Donor Marker*	All Patients	Patients Who Seroconverted
	no.	*no. (%)*
Anti-HCV–negative		
No surrogate markers	31	4 (13)
ALT ≥45 IU/liter, anti-HBc, or both	8	0 (0)
Anti-HCV–positive		
No surrogate markers in same unit†	15	14 (93)
ALT ≥45 IU/liter, anti-HBc, or both in same unit‡	45	41 (91)

*Anti-HCV–positive refers to the results of both first- and second-generation tests. ALT denotes alanine aminotransferase.

†Two recipients received one other unit that was positive for a surrogate marker only.

‡Nine recipients received one other unit that was positive for a surrogate marker only.

of patients for whom a well documented medical history is available may be limited

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the second-generation assay increased this rate to 93 percent. Four transfusion recipients with HCV received blood that was negative according to both the first- and second-generation assays and was negative for the surrogate markers as well. Thus, the residual incidence of HCV predicted after first-generation screening (0.9 percent, or 11 of 1232) would have been reduced to 0.3 percent (4 of 1232) by screening donors with the second-generation assay and would not have been further reduced by screening for surrogate markers.

The prediction of a continuing risk of HCV infection from blood transfusion is not surprising in view of studies in chimpanzees that document infectivity before the onset of hepatitis.[19,20] We observed the development of non-A, non-B hepatitis in two chimpanzees inoculated with serum collected from recipients at least 12 days before any biochemical evidence of hepatitis.[19] Recent studies using gene amplification to detect HCV nucleic acid have also demonstrated viremia within a few days after exposure and weeks before the development of either hepatitis or an antibody response.[21]

The data presented here raise the question of whether we should continue to test donors for surrogate markers. The delay in the appearance of anti-HCV after the increase in alanine aminotransferase levels in acute HCV suggests that it may be advantageous to continue screening donors for high alanine aminotransferase concentrations until tests are available to detect infection before the onset of hepatitis. Our finding of no anti-HCV seroconversions after transfusion with blood that had only an elevated alanine aminotransferase level suggests that this occurs infrequently. Continued anti-HBc screening may also be advantageous because it can identify some donors with HBV infection not detected by routine HBsAg testing.[22]

The results of this study indicate that donor screening for the presence of surrogate markers and, more recently, for anti-HCV by first-generation assays should have substantially reduced the risk of non-A, non-B post-transfusion hepatitis. They also indicate that the risk will be further reduced by implementation of second-generation anti-HCV screening. In our study, the rate of 3.6 percent for non-A, non-B post-transfusion hepatitis not caused by HCV was not significantly different from the rate of hepatitis observed among control subjects who did not undergo transfusion.

We are indebted to the members of the independent expert committee: Drs. Paul Holland, William H. Bancroft, Allan G. Redeker, and Hyman J. Zimmerman.

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