

CLINICAL OUTCOMES AFTER HEPATITIS C INFECTION FROM CONTAMINATED ANTI-D IMMUNE GLOBULIN

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ABSTRACT

Background and Methods In February 1994, batches of anti-D immune globulin used in Ireland during 1977 and 1978 to prevent Rh isoimmunization were found to be contaminated with hepatitis C virus (HCV) from a single infected donor. In March 1994, a national screening program was initiated for all women who had received anti-D immune globulin between 1970 and 1994. Of the 62,667 women who had been screened when this study began, 704 (1.1 percent) had evidence of past or current HCV infection, and 390 of those 704 (55 percent) had positive tests for serum HCV RNA on reverse-transcription-polymerase-chain-reaction analysis. All 390 were offered a referral for clinical assessment and therapy. We evaluated 376 of these 390 women (96 percent); the other 14 were not seen at one of the designated treatment centers.

Results The mean (\pm SD) age of the 376 women was 45 ± 6 years at the time of screening. They had been infected with hepatitis C for about 17 years. A total of 304 women (81 percent) reported symptoms, most commonly fatigue (248 women [66 percent]). Serum alanine aminotransferase concentrations were slightly elevated (40 to 99 U per liter) in 176 of 371 women (47 percent), and the concentrations were 100 U per liter or higher in 31 (8 percent). Liver biopsies showed inflammation in 356 of 363 women (98 percent); in most cases the inflammation was slight (41 percent) or moderate (52 percent). Although the biopsy samples from 186 of the 363 women (51 percent) showed evidence of fibrosis, only 7 women (2 percent) had probable or definite cirrhosis. Two of the seven reported excessive alcohol consumption.

Conclusions Most of the women with HCV infection 17 years after receiving HCV-contaminated anti-D immune globulin had evidence of slight or moderate hepatic inflammation on liver biopsy, about half had fibrosis, and 2 percent had probable or definite cirrhosis. (N Engl J Med 1999;340:1228-33.)

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IDENTIFICATION in 1989 of hepatitis C virus (HCV) as the main causative agent of non-A, non-B hepatitis¹ was followed by the recognition of a high prevalence of HCV infection after transfusion of infected blood or blood products and in association with intravenous drug abuse.²⁻⁸ The availability of increasingly sensitive and reliable techniques to screen blood for HCV has substantially reduced the incidence of post-transfusion hepati-

tis.⁹⁻¹² Because prospective studies are time-limited, retrospective studies of iatrogenic HCV infection are the main source of information on the natural history of the disease over an extended period.¹³

Routine screening of blood donors for HCV antibodies commenced in Ireland in October 1991. A regional study of donors, carried out from October 1991 to February 1994, identified 14 men and 15 women with HCV antibodies. These 15 women differed substantially from the overall donor population; they were older, and 13 of them (87 percent) were Rh-negative, as compared with a rate of 18 percent in the general population.^{14,15} Twelve of these 15 women had received anti-D immune globulin in 1977. HCV (genotype 1b) contamination of the anti-D immune globulin given in 1977 and 1978 was confirmed by reverse-transcription-polymerase-chain-reaction analysis of stored samples of the preparation.¹⁶ The information already available on the consequences of this contamination is shown in Table 1.

This discovery provoked a major health care crisis, particularly in relation to the operation of the autonomous Irish Blood Transfusion Service Board. Four steps were taken to establish the precise cause of the contamination of anti-D immune globulin and to address the consequences for the infected women. These were the establishment of a national screening program in February 1994 (under the direction of the Irish Blood Transfusion Service Board) for all recipients of anti-D immune globulin from its introduction in the early 1970s until February 1994, the referral of all the women who were positive for HCV to one of six hepatology centers, the establishment by the government of a group of experts in March 1994¹⁶ and a national tribunal of inquiry in October 1996¹⁷ to investigate the circumstances and consequences of the contamination, and the creation of the Hepatitis C Compensation Tribunal to expedite the processing of related claims by infected women.¹⁸ Screening was carried out by means of an enzyme-linked immunosorbent assay. Women with positive tests were further evaluated with the use of a recombinant immunoblot assay, and a reverse-trans-

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TABLE 1. INFORMATION AVAILABLE ON THE CONSEQUENCES OF USING HCV-CONTAMINATED ANTI-D IMMUNE GLOBULIN.*

Report of the Expert Group (January 1995)	
VARIABLE	FINDING
Estimated percentage of anti-D immune globulin recipients who were screened	94
No. of women with HCV antibody (1970–1994)	1037
No. of women with HCV RNA (1970–1994)	455
Report of the Tribunal of Inquiry (March 1997)	
October 4, 1976, to January 4, 1977: plasma from one donor was used to prepare five batches of anti-D immune globulin	
November 4, 1976: donor had a reaction to a transfusion	
November 17, 1976: donor became jaundiced, and hepatitis was diagnosed	
January 10 to 19, 1977: additional supplies of plasma were obtained from the donor	
February 14 to July 4, 1977: these supplies were used in preparing 16 batches of anti-D immune globulin; 8 of these batches have been confirmed to have been positive for HCV RNA	
VARIABLE	FINDING
No. of women screened	62,667
Variation in no. of doses per batch	250 to >400
No. of doses prepared from infected batches	
Lower estimate: 250 in each of 8 boxes	2000
Upper estimate: 400 in each of 16 boxes	6400
Estimated no. of exposed women screened (based on 100% use of doses, 94% screening)	1880–6016
Total no. of screened women with HCV antibody	704
No. with HCV antibody and HCV RNA	390
No. with HCV antibody only	314
Estimated no. of exposed women without HCV antibody	1176–5312

*As of March 1999, the Irish Blood Transfusion Service Board had not provided definitive information on the number of women exposed to HCV-contaminated anti-D immune globulin in 1977 and 1978 and on the number of such women who have been screened.

scription–polymerase-chain-reaction assay was used to confirm the presence of HCV RNA.

The tribunal of inquiry concluded that contamination of anti-D immune globulin in 1977 and 1978 was the consequence of including plasma from a woman who had received a diagnosis of infective hepatitis in a pool of blood products from which the product was manufactured.¹⁷

The Hepatitis C Compensation Tribunal was established in May 1997 to “award compensation to certain persons who have contracted hepatitis C within the state from anti-D immunoglobulin, other blood products or blood transfusion and to provide for connected matters.”¹⁸ As of November 1998, 1871 claims had been made to the compensation tribunal; awards were agreed on in 1042 cases (not all the hepatitis C infections were related to contaminated anti-D immune globulin), and a total of \$219 million in compensation was paid.

To date, the Irish Blood Transfusion Service Board has not disclosed information about the percentage of recipients of contaminated anti-D immune glob-

ulin in 1977 or 1978 who have been screened or the percentage of such women who have been found to be negative for HCV antibody. However, the rate of screening is probably extremely high: the overall participation rate was estimated to be 94 percent of women who had received anti-D immune globulin between 1970 and 1994,¹⁶ and available national mortality data for the age and sex cohort affected do not reveal an increase in liver-related deaths from 1977 onward.¹⁹ Furthermore, the high level of public awareness of the issue combined with the average compensation of \$210,173 per claimant probably ensured a high degree of participation in the screening program. Available data suggest that substantially more than half the recipients of the contaminated anti-D immune globulin in 1977 and 1978 were negative for HCV antibody 17 years later (Table 1).

Research to date on this outbreak has been carried out independently by the Irish Blood Transfusion Service Board^{14,15} and the six designated treatment centers.^{20,21} In this report, we present the results of the clinical evaluation of all HCV RNA–positive women referred from the screening program who were seen at the six centers.

METHODS

Patients

As of March 1997, 62,667 women had presented for screening (56,151 in 1994, 2636 in 1995, 3696 in 1996, and 184 in 1997).¹⁷ Among the screened women who had received anti-D immune globulin in 1977 or 1978, 704 had positive tests for HCV antibody, and 390 of those 704 (55 percent) had positive tests for HCV RNA. The present study describes 376 of these 390 women (96 percent). Although all 390 women were offered a referral for clinical assessment and therapy, 14 were not seen at any of the six designated treatment centers. Each woman for whom viral typing or subtyping was available had a genotype of 1 or 1b.

The women were examined clinically by standard methods, and no research protocol was involved. Therefore, approval from the institutional review boards of the participating centers was not obtained. Written informed consent was obtained from all the women before they underwent liver biopsy.

Data Collection

For each woman, we obtained data on risk factors for HCV infection as well as the obstetrical, medical, and surgical history, and each woman underwent a physical examination. Information about alcohol consumption was obtained; excessive intake was defined as the consumption of 14 or more units of alcohol per week (where 1 unit equals 10 g of alcohol).²² Serum alanine aminotransferase was measured in 371 women, ultrasonography of the liver and biliary tree was performed in 174, and liver biopsies were performed in 363. The laboratory data were recorded only at the initial examination, whereas the clinical information was obtained at both the initial and the follow-up examinations.

Histologic Studies

Pathologists who were aware of the women’s HCV status assessed the liver-biopsy samples and classified the findings as recommended by the International Association for the Study of the Liver²³ and other working parties.^{24,25} Inflammation was graded and the stage of fibrosis assessed (by Masson’s trichrome staining)

in separate steps. Each pathologist evaluated a representative cross section of samples according to a standardized scoring system, with every fifth sample assessed jointly by two pathologists. Inflammation was graded on a cumulative 18-point scale, with interface change or piecemeal necrosis graded from 0 to 4, confluent necrosis from 0 to 6, lobular inflammation from 0 to 4, and portal inflammation from 0 to 4.²³ Fibrosis was classified according to the following scale: 0 indicated no fibrosis, 1 periportal or portal fibrosis, 2 portal-portal bridging, 3 portal-central bridging with or without early nodule formation, and 4 probable or definite cirrhosis.

Recombinant Immunoblot, Polymerase-Chain-Reaction, and Genotyping Studies

Screening for HCV antibody was carried out by means of a third-generation enzyme-linked immunosorbent assay (Abbott, Wiesbaden, Germany). Women whose test results were positive were further evaluated with the use of a third-generation recombinant immunoblot assay (Ortho Diagnostic Systems, Chiron, Emeryville, Calif.). For this assay, recombinant HCV-encoded antigens (C33 and NS5) and synthetic HCV-encoded peptides (C22 and C100) were immobilized as individual bands on test strips. The bands were then scored on a six-point scale, where a minus sign represents absent, \pm indeterminate, and 1+ to 4+ increasingly positive. The overall test result was considered to be negative when none of the bands had 1+ or greater reactivity, indeterminate when just one band had reactivity scored as 1+ or greater, and positive when two or more bands had reactivity scored as 1+ or greater.

HCV RNA status was established in a single laboratory. Segments of the HCV genome were amplified by the polymerase chain reaction. HCV genotyping was performed by restriction-fragment-length polymorphism analysis of sequences in the 5' noncoding region.^{26,27}

Statistical Analysis

Most analyses involved the use of standard descriptive statistical techniques. The relation between ordinal variables was estimated with Kendall's rank-correlation coefficient. Analysis of covariance was also used. All statistical tests were two-tailed.²⁸ The statistical software package used was SPSS for Windows (SPSS, Chicago).

RESULTS

At the initial assessment, the 376 women ranged in age from 34 to 60 years (mean [\pm SD], 45 \pm 6). Thus, the mean age was approximately 28 years at the probable time of HCV infection (in 1977 or 1978). The mean number of births per woman was 4 \pm 2 (range, 1 to 13). Information with regard to HCV type and subtype was available for 360 and 157 women (96 percent and 42 percent), respectively; type 1 or 1b was identified in all cases.

Subjects

A total of 304 women (81 percent) reported one or more symptoms during the review period. The most common symptoms were fatigue (248 women [66 percent]), arthralgia or myalgia (143 [38 percent]), anxiety or depression (60 [16 percent]), right-upper-quadrant pain (23 [6 percent]), and rashes (19 [5 percent]). Gallstones were detected in 33 (19 percent) of the 174 women who underwent ultrasonography. The most common problems noted in medical histories were classified as follows: nonhepatic gastrointestinal (45 women [12 percent]), he-

TABLE 2. HISTOLOGIC GRADE OF HEPATIC INFLAMMATION AND STAGE OF FIBROSIS IN RELATION TO SERUM ALANINE AMINOTRANSFERASE CONCENTRATIONS IN 363 WOMEN WITH HCV INFECTION.*

VARIABLE	NO. OF WOMEN (%)	SERUM ALANINE AMINOTRANSFERASE CONCENTRATION†	
		MEDIAN	RANGE
		U/liter	
Grade of inflammation			
0	7 (2)	24	11-66
1-3	150 (41)	37	10-261
4-8	190 (52)	46	10-232
9-18	16 (4)	80	34-381
Stage of fibrosis			
No fibrosis	177 (49)	35	10-198
Periportal or portal fibrosis	124 (34)	46	10-261
Portal-portal bridging	36 (10)	53	15-381
Portal-central bridging	19 (5)	100	34-232
Probable or definite cirrhosis	7 (2)	56	17-218
All patients	363	42	10-381

*Because of rounding, not all percentages total 100. There was a significant correlation between the grade of inflammation and the serum alanine aminotransferase concentration ($r=0.23$, $P<0.001$) and between the stage of fibrosis and the serum alanine aminotransferase concentration ($r=0.30$, $P<0.001$).

†The upper limit of the normal range is 40 U per liter.

patic (44 [12 percent]), respiratory (34 [9 percent]), obstetrical or gynecologic (30 [8 percent]), cardiovascular (29 [8 percent]), and psychological (26 [7 percent]). The most frequent surgical procedures were obstetrical or gynecologic procedures (135 women [36 percent]), appendectomy (56 [15 percent]), cholecystectomy (34 [9 percent]), and tonsillectomy (29 [8 percent]).

Approximately one third of the women had at least one other risk factor for hepatitis in addition to exposure to contaminated anti-D immune globulin; the most common of these other risk factors were previous blood transfusions (64 women [17 percent]), previous acupuncture treatments (19 [5 percent]), tattoos (4 [1 percent]), and intravenous drug use (3 [1 percent]). Seventeen (5 percent) of the 338 women for whom information on alcohol consumption was available reported that they drank 14 or more units of alcohol weekly. Forty-one (11 percent) of the 376 women had been blood donors (25 after 1977).

Serum Alanine Aminotransferase Concentrations and Histologic Findings

Serum alanine aminotransferase concentrations were slightly elevated (40 to 99 U per liter) in 176 (47 percent) of 371 women and more highly elevated (≥ 100 U per liter) in 31 (8 percent) of the women. Of the 363 women who had liver biopsies, 356 (98 percent) had inflammation (Table 2); 150 (41 per-

cent) of the 363 had minimal inflammation (score, 1 to 3), and 190 (52 percent) had chronic mild hepatitis (score, 4 to 8), with predominantly periportal and portal or lymphocytic inflammation. Confluent necrosis was present in 7 (2 percent) of the 363 biopsy specimens. Specimens from 186 women (51 percent) showed evidence of fibrosis, ranging from periportal or portal only (124 women [34 percent]) to probable or definite cirrhosis (7 women [2 percent]). Two of these seven women reported excessive alcohol consumption (14 or more units per week); none had other identified risk factors for serious liver disease. The histologic grade of inflammation and the stage of fibrosis were significantly correlated ($r=0.45$, $P<0.001$). There was a significant relation ($P<0.001$) between serum alanine aminotransferase concentrations and both the histologic stage of fibrosis and the grade of inflammation (Table 2).

HCV Infection Status

The results of recombinant immunoblot assay were available for 316 women; in some cases, the results were incomplete. Whereas the outcome was almost invariably 4+ for C22 (301 of 313 women [96 percent]) and C33 (304 of 314 [97 percent]), the corresponding rates were lower for both C100 (231 of 314 [74 percent]) and NS5 (192 of 305 [63 percent]). Seventy-five of 305 test results were negative or indeterminate for NS5. However, neither serum alanine aminotransferase concentrations nor histologic status was significantly influenced by the results for C100 and NS5.

DISCUSSION

This study, involving 376 women who had been infected with HCV 17 years earlier, indicates that the virus causes a slowly progressive liver disease. The insidiousness of the development of the disease is evident from the elevated serum alanine aminotransferase concentrations in 55 percent of the women and biopsy evidence of inflammation in 98 percent and fibrosis in 51 percent. The increased frequency of detection of the C22 and C33 antigens of HCV is consistent with the results of previous studies of HCV type 1 infection.²⁹

Symptoms, which were reported by 81 percent of the women, consisted mainly of fatigue (66 percent), arthralgia or myalgia (38 percent), and anxiety or depression (16 percent). It is important to note that the screening program was carried out during the highly publicized public health controversy that followed disclosure of the outbreak. Thus, the high frequency of symptoms may have been influenced to some degree by the women's increased awareness of the potential consequences of HCV infection.²⁰ Because we did not include a matched control group, we cannot estimate the extent to which reported symptoms were associated with HCV infection.

Reliably determining the prognosis is a major challenge in the care of patients with infection.³⁰⁻³² Although the lack of comprehensive longitudinal studies has severely limited progress in this regard, the individual and interactive influences of several putative prognostic factors have been examined.^{3,5,6,33} These include age, sex, immune status, duration of disease, route of transmission of the virus, volume of the infected dose, and viral genotype. The situation is complicated by variations in the interval between the time of the infection and the time of the prognostic evaluation. Factors such as current viral load and histologic status have been identified as potentially important in determining the prognosis and, in particular, the likelihood of a sustained response to therapy.^{8,34}

The mode of transmission of HCV may offer a particularly useful insight into the prognosis. For example, a generally poor outcome was reported for a group of patients with hypogammaglobulinemia who had iatrogenic HCV infection,^{5,6} whereas patients with infection as a result of intravenous drug use had a more favorable outcome.^{8,34,35} The consequences of transfusion-induced HCV infection vary substantially among studies. In a group of patients with hepatitis C acquired, in most cases, after transfusion associated with cardiac surgery, who were followed for a mean of 90 months, 21 of 65 patients who underwent liver biopsy (32 percent) had cirrhosis.³³ However, in a group of patients with acute non-A, non-B hepatitis after transfusion who were followed for an average of 18 years, mortality rates were similar to those for matched, noninfected transfusion recipients.³⁶

A German study of 152 women infected with HCV-contaminated Rh₀(D) immune globulin is particularly relevant to our study.⁴ After 15 years, none of these women had chronic active hepatitis or cirrhosis. Although we found a pattern of more progressive disease 17 years after infection, the overall rate of serious liver disease was relatively low in our study. The likelihood that most of the women who received contaminated anti-D immune globulin in Ireland during 1977 or 1978 did not have HCV antibody or viremia 17 years after infection is consistent with this observation. Our finding that only 55 percent of women with positive tests for HCV antibody also had positive tests for HCV RNA contrasts with an estimate of 86 percent in a group of 248 blood donors with positive antibody tests.³⁷

For the main modes of viral transmission, efforts have been made to identify the nonetiologic factors that influence the prognosis. In a study of patients with HCV infection resulting from transfusion, the viral load was not related to the patient's age at infection, sex, or biochemical profile.³⁴ Inflammatory activity on histologic examination has been reported to be greater in cases of transfusion-acquired HCV

infection than in cases of infection related to intravenous drug abuse, but the age at biopsy, sex, and duration of disease were not predictive of such activity.⁸ However, the suggestion that the prognosis is independent of age is not universally accepted.^{3,33,38} One study, for instance, found that although the rates of progression to chronic hepatitis, cirrhosis, and hepatocellular carcinoma in young patients (average age, 29 years) were similar to those in older patients (average age, 58 years), the average time from infection to the development of each of these sequelae was more than twice as long in the younger patients.³

The influence, if any, of genotype on disease progression is unclear. HCV type 1 infection responds less often to treatment with interferon alfa than does infection with HCV type 2 or 3.³⁹ However, a longitudinal study of untreated patients failed to identify an association between the progression of fibrosis and the HCV genotype after controlling for age, sex, and alcohol intake.³⁸ In that study, the rate of disease progression was lower in women than in men, a finding consistent with the more rapid elimination of HCV from serum in women.⁴⁰ The size of the infecting dose of virus may also be an important factor, since the volume of contaminant would be considerably less in anti-D immune globulin than in transfused blood.

In conclusion, we evaluated the consequences of iatrogenic HCV infection in a relatively homogeneous group of women who were infected during their childbearing years, about 17 years earlier. Although almost all the women who underwent liver biopsy had evidence of inflammation, only about half had some degree of fibrosis and only 2 percent had probable or definite cirrhosis.

APPENDIX

Other members of the Irish Hepatology Research Group were as follows: S. Albloushi (Beaumont Hospital, Dublin), G. Callagy (Mater Misericordiae Hospital, Dublin), G.M. Courtney (Beaumont Hospital), J. Crowe (Mater Misericordiae Hospital), M. Crowley (Statistical Laboratory, University College Cork), C. Devereux (Statistical Laboratory, University College Cork), R. Farrell (St. James's Hospital, Dublin), J. Hegarty (St. Vincent's Hospital, Dublin), E. Kay (Beaumont Hospital), D. Kelleher (St. James's Hospital), P. Kelly (Mater Misericordiae Hospital), M. Leader (Beaumont Hospital), M. Little (University College Hospital, Galway), C. McCarthy (University College Hospital), G. McDonald (St. James's Hospital), J. McWeeney (University College Hospital), F. Murray (Beaumont Hospital), N. Nolan (St. Vincent's Hospital), T. O'Gorman (University College Hospital), C.J. O'Keane (Mater Misericordiae Hospital), R. Pilkington (St. James's Hospital), D. Royston (Beaumont Hospital), F. Shanahan (Cork University Hospital), M. Sheehan (Cork University Hospital), D. Weir (St. James's Hospital), and M. Whelton (Cork University Hospital).

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