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## The natural history of chronic hepatitis C in haemophiliacs

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**Summary.** Most haemophiliacs treated with non-virally-inactivated clotting factor concentrates have been infected with hepatitis C virus (HCV). We have studied the natural history of chronic HCV infection by following all 138 HCV-positive patients from our centre for periods of up to 28 years. As well as the clinical and biochemical characteristics, we studied 116 liver samples from 63 patients obtained at elective biopsy ( $n = 103$ ) or autopsy ( $n = 13$ ). 36 (26%) of the patients were HIV positive, and three were chronic carriers of hepatitis B. Evidence of previous exposure to hepatitis A and B was found in 37.2% and 48.1% respectively. Raised transaminase levels were found in 82.6% of patients. 11 of 15 patients with normal transaminases tested by PCR for HCV RNA were positive, indicating that most patients, even in this group, have chronic hepatitis C infection. Cirrhosis was diagnosed by

liver histology in 19 patients, and nine patients developed liver failure. The incidence of cirrhosis rose rapidly 15 years after HCV infection to 15.6 per 1000 person-years. Multivariate analysis showed that HIV status, length of time since HCV infection and age at HCV infection were independently associated with both the development of cirrhosis and liver failure. Two patients developed hepatocellular carcinoma; one of these was exposed only to a single batch of FVIII concentrate 11 years earlier. Chronic hepatitis C is increasingly recognized as a major cause for morbidity and mortality in haemophiliacs, especially those who are HIV positive and who were infected at an older age.

**Keywords:** hepatitis C, HCV, natural history, haemophilia, liver disease.

For more than 20 years it has been known that some haemophiliacs treated for the first time with clotting factor concentrates developed jaundice with biochemical evidence of hepatitis (Kasper & Kipnis, 1972). Two studies from England showed that the incidence of biochemical liver abnormalities after first exposure was virtually 100% (Fletcher *et al.*, 1983; Kernoff *et al.*, 1985). In the absence of serological markers for hepatitis A or B the aetiological agent was called non-A, non-B (NANB). In 1989 the virus responsible was cloned and named hepatitis C (Choo *et al.*, 1989). Since 1985, clotting factor concentrates have undergone viral inactivation, but almost all patients treated prior to this have been infected with HCV (Makris *et al.*, 1990).

Acute HCV hepatitis is often a trivial event: the clinical importance of HCV infection lies in its propensity to progress to histologically proven chronic liver disease. Prospective studies in non-haemophiliacs with acute non-A, non-B hepatitis reveal that approximately 50% of these subjects will exhibit liver enzyme abnormalities characteristic of

chronic hepatitis (Mattsson *et al.*, 1988; Di Bisceglie *et al.*, 1991; Seef *et al.*, 1992). Histological examination of the liver in patients with chronic hepatitis has revealed that 15–25% of the patients have established cirrhosis (Mattsson *et al.*, 1988; Di Bisceglie *et al.*, 1991; Seef *et al.*, 1992; Alter, 1989).

Despite the histological progression, the clinical features of chronic liver disease are often unremarkable and the eventual impact of chronic HCV on morbidity and mortality remains to be established. The relatively benign nature of chronic post-transfusion hepatitis was emphasized by Seef *et al.* (1992), who, in a prospective study, reported no increased mortality among subjects with transfusion-associated NANB hepatitis for up to 18 years after the initial infection. A small but statistically significant increase in the number of deaths related to liver disease was, however, noted.

Recently two publications have reported the rapid progression of HCV to end-stage liver failure in haemophiliacs, but in both reports this progression appeared to occur almost exclusively in patients co-infected with the HIV virus (Eyster *et al.*, 1993; Telfer *et al.*, 1994). The lack of progression in the HIV-negative patients is in contrast to other studies reporting liver failure deaths in recipients of blood transfusion after intervals of 20 years.

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Here we report the natural history of HCV infection and the progression of chronic HCV-related liver disease in a cohort of haemophiliacs studied prospectively for periods of up to 28 years since their first exposure to hepatitis C through clotting factor concentrates.

#### PATIENTS AND METHOD

*Patients.* The cohort of 138 patients in this study constitutes all the known hepatitis C antibody positive patients with hereditary haemorrhagic disorders treated in Sheffield, U.K. 132 received non-virally inactivated concentrates in the period 1968–85, four received heat-treated products clearly implicated in HCV transmission (Makris *et al.*, 1993) and two received only virally inactivated FVIII but prior to 1985 received large quantities of cryoprecipitate.

*Follow-up.* Patients with severe haemophilia (A and B) were reviewed at least three times a year, whilst others (including those with von Willebrand's disease) were reviewed annually. HIV-positive patients were reviewed at least 3-monthly. Recently all HCV antibody positive patients have also been reviewed 4-monthly. Liver enzyme estimation was performed at each visit.

*Liver biochemistry tests.* Liver enzyme determinations (Alanine [ALT] and aspartate [AST] aminotransferase) were performed on each individual at every visit. The pattern of liver enzyme abnormality was assessed on the last three ALT estimations and was considered persistently abnormal if all three estimates were abnormal and intermittently abnormal if one or two were abnormal. In patients treated with interferon, the pattern of enzyme abnormalities just prior to the commencement of therapy was recorded.

*Date of HIV infection.* For HIV-positive patients, the date of HIV seroconversion was determined from stored sera and taken to be the midpoint of the interval between the last negative and first positive test. For patients for whom no negative test was available, the midpoint of the interval between 10 June 1981 (the date of the first HIV-positive test in a Sheffield haemophiliac) and the date of the first positive test was calculated. For patients who moved to Sheffield after a diagnosis of HIV was made in another centre the date of seroconversion was assumed to be 9 February 1983 (the midpoint between the first and last seroconversion in Sheffield haemophiliacs).

*Date of HCV infection.* This was assumed to be the date of the patient's first exposure to clotting factor concentrate prepared from pooled donations. In 25% of cases when this was unknown the date of infection was taken to be 1 January 1972 (the date of widespread introduction of concentrates in our centre); for persons born after this date it was taken to be the date of their first birthday.

*Histology.* The criteria for performance of liver biopsy over the period 1977–94 varied, and although most biopsies were originally performed in patients with persistently abnormal liver enzymes, later biopsies were also performed in other patient groups. Liver biopsies were performed after correction of the bleeding disorder as previously described (Makris *et al.*, 1991). All liver histology was interpreted by a

single experienced histopathologist (J.C.E.U.) using standard criteria. Two patients who died of liver failure without formal examination of liver tissue were assumed to have had cirrhosis at the time of death. In three patients who underwent liver transplantation, only liver histology of the original liver is included.

*Definition of hepatic decompensation.* Hepatic decompensation was defined as the presence of two of the following: ascites, jaundice, prolonged prothrombin time or hepatic encephalopathy. Ascites was detected clinically (this was marked in each case), jaundice was defined as a bilirubin concentration greater than twice the upper limit of normal, prothrombin time prolongation was accepted if it was more than 5 s above the upper limit of normal (normal range 11–15 s). Oesophageal varices were detected endoscopically or radiologically and hepatocellular carcinoma was confirmed histologically.

*Virology tests.* HCV was detected with a second-generation ELISA test (Orlho Diagnostics). HBsAg, anti-HBc and anti-HBs tests were performed using standard techniques. All positive HIV ELISA tests were confirmed with the Western blot technique. HCV RNA was detected with PCR as previously described (Preston *et al.*, 1995b).

*Statistics.* The risk of cirrhosis and liver failure over time since infection with HCV was estimated by the Kaplan-Meier life-table method. Briefly, with this method the probability of event-free (cirrhosis or liver failure) survival over the follow-up time is calculated, taking censoring into account.

We calculated the incidence of cirrhosis by the patient-year method. Here, we computed the time of follow-up for each patient, i.e. the elapsed between the date of HCV infection and either end of study, or cirrhosis, or death, whichever came first. The overall incidence was then found by adding the total patient-time of the cohort, and dividing the total number of cirrhotic events by the total patient-time. To investigate whether the incidence varied with the time elapsed since infection, we stratified the total follow-up time in periods since infection: 0–4 years since HCV infection, 5–9 years, 10–14 years and 15+ years since HCV infection. By taking into account in which period each cirrhotic event occurred, we calculated incidence rates for each of these periods (e.g. if a patient developed cirrhosis 8 years after HCV infection, he would contribute 5 years to the first, and 3 years to the second period, and his cirrhosis would be counted in the numerator of the second period). Incidences for time since infection were calculated for liver failure in the same way. A 95% confidence interval (CI 95) was based on a Poisson distribution for the outcome variable.

A Cox proportional hazards model was used to assess the effect of several other factors on the risk of cirrhosis and liver failure. This multivariate model allows for estimating the effect of several risk factors, while controlling for possible time trends in the baseline incidence which is allowed to vary, and adjusted for other factors. For each factor the model yields a hazard ratio, which can be viewed as the ratio of the incidence in the presence of that factor over the incidence in the absence of that factor (which itself is allowed to vary over time), adjusted for all other factors in the model.



As covariates we used severity of haemophilia (mild, moderate, severe), HIV status (negative positive) and age at HCV infection (in actual years and in classes 0–4 years, 5–9 years, 10–19 years, 20–29 years, 30–39 years, and 40+ years) A hazard ratio of 1 indicated an equal risk in the presence or absence of the factor of interest, a hazard ratio of > 1 indicated an increased risk associated with that factor

## RESULTS

### Patient characteristics

The cohort of 138 patients represents all the patients in Sheffield with bleeding disorders diagnosed as being HCV positive up to January 1995. The mean age of the patients was 38.25 years with a range of 11.1–87.2 years (Table I). Total follow-up of the cohort was for 2596.7 person years since infection with hepatitis C. 127 of the patients were male and in 71 the bleeding disorder was severe (FVIII/IX < 0.02 IU/ml). 121 patients had either haemophilia A or B, 10 patients suffered from von Willebrand's disease, five were haemophilia carriers, and two suffered from factor X deficiency and were treated with non-virally inactivated prothrombin complex concentrates.

**Table I.** Clinical characteristics of the whole cohort of 138 HCV-positive patients and of the 63 patients on whom liver histology was available

	All patients <i>n</i> = 138 (%)	Liver histology patients <i>n</i> = 63 (%)
Age		
Median	38.25	44.1
Range	11.1–87.2	18.3–78.0
Sex		
Male	127 (92)	61 (96.8)
Female	11 (8.0)	2 (3.2)
Diagnosis		
Haemophilia A	97 (70.3)	51 (81)
Haemophilia B	24 (17.4)	8 (12.7)
von Willebrand's disease	10 (7.2)	2 (3.2)
Other	7 (5.1)	2 (3.2)
Severity of bleeding disorder		
0.000–0.009 IU/ml	18 (13.0)	8 (12.7)
≤ 0.01 IU/ml	71 (51.4)	33 (52.3)
0.02–0.05 IU/ml	15 (10.9)	6 (9.5)
≥ 0.055 IU/ml	50 (36.2)	24 (38.1)
ALT abnormality		
Persistent	76 (55.1)	44 (69.8)
Intermittent	39 (28.3)	14 (22.2)
Normal	24 (17.4)	5 (7.9)
Co-infection		
Anti-HIV positive	36 (26.1)	26 (41.3)
HBsAg positive	3 (2.2)	2 (3.2)
No dead	26 (18.8)	20 (31.7)

### Age of HCV infection

Patients were infected with HCV at a mean age of 21.66 (range 0.06–79.32 years). The following number of patients were infected in the different age groups: 0–4 years, 26; 5–9 years, 20; 10–19 years, 27; 20–29 years, 28; 30–39 years, 14; 40+ years, 23.

### Infection with other viruses

Thirty-six patients (26.1%) were HIV positive, of whom 17 (47.2%) have died. 35/94 (37.2%) patients were hepatitis A IgG positive, indicating past infection with this virus. Only three patients are currently infected with the hepatitis B virus (i.e. HBsAg positive) but 65/135 (48.1%) had evidence of previous exposure to this virus (anti-HBc positive or anti-HBs positive in the unvaccinated patients).

### Liver function tests

Seventy-seven of 138 (55.8%) patients had persistently abnormal transaminase levels, 37 (26.8%) had intermittently abnormal levels and in 24 (17.4%) all the last three transaminases were normal. 15 patients from the group with normal ALT were tested for HCV RNA using nested PCR (Preston *et al*, 1995b) and 11 of these were found to be positive, indicating active viraemia rather than immunity. Histology was available on five members of this normal transaminase group, this showed cirrhosis in two, chronic active hepatitis (CAH) in one and chronic persistent hepatitis (CPH) in two.

### Liver biopsies

Histology was available from 63 cohort patients. Patients had one to five liver biopsies. In 13 patients who died, histology was obtained either by full (*n* = 8) or limited (*n* = 5) autopsy.

All liver histology was abnormal. All biopsies showed chronic hepatitis with varying severity. Using histopathological standard criteria and nomenclature at the time of biopsy, 37/63 (58.7%) of initial biopsies showed chronic persistent hepatitis and 23/63 (36.4%) showed chronic active hepatitis or cirrhosis. Most biopsies also exhibited features associated with HCV infection, such as steatosis, sinusoidal infiltration by leucocytes and portal lymphocytic aggregates. 29 patients had more than one liver biopsy. Cirrhosis was found in the most recent liver biopsy of 19 patients and liver failure occurred in nine patients. Table II details the data from the 19 patients with cirrhosis.

The mean time from HCV infection to the development of cirrhosis was 18.58 (range 3.02–26.65 years). For liver failure the mean was 19.15 (range 7.81–28.05 years). Overall the incidence of cirrhosis was 7.54 per 1000 person-years following HCV infection but it increased markedly from 2.9 per 1000 person-years in the first 5 years following infection to 15.6 per 1000 person-years after > 15 years following HCV infection had elapsed (Table III). No patient showed signs of liver failure within 4 years of HCV infection, but after this period the number of patients developing liver failure was fairly constant at a mean incidence of 3.47 per 1000 person-years.

Fig 1 shows a Kaplan Meier plot for the development of cirrhosis and liver failure from the time of HCV infection. 22

Table II Characteristics of patients with hepatic decompensation or cirrhosis

Patient	Diagnosis	Severity (iu/ml)	Age at HCV infection (yr)	Age at HIV infection (yr)	Age at biopsy of cirrhosis (yr)	Age at hepatic decompensation (yr)	Age at outcome (yr)
015	Haemophilia B	0.05	65.4	NA	78.0	77.9	Dead 78.0
064	Haemophilia A	0.03	63.9	70.5	71.8	71.8	Dead 72.2
027	Haemophilia A	0.07	57.0	66.9	70.6	NA	Dead 70.6
006	Haemophilia A	0.09	55.2	NA	NA	33.7	Dead 77.6
104	Haemophilia A	0.07	48.0	NA	51.0	58.7	Transplant 63.2
125	Haemophilia A	0.01	48.0	60.9	55.1	NA	Dead 65.1
098	Haemophilia A	0.01	46.6	NA	53.5	54.5	Dead 55.1
010	Haemophilia A	0.10	41.8	NA	44.8	NA	Transplant 57.7
116	von Willebrand's disease	0.18	34.4	NA	38.4	NA	Alive 51.5
056	Haemophilia A	0.01	34.2	38.3	NA	43.3	Dead 43.6
123	Haemophilia A	0.10	29.8	NA	45.0	NA	Alive 51.9
042	Haemophilia A	0.01	26.8	NA	42.3	NA	Alive 48.7
072	Haemophilia A	0.01	25.7	37.3	45.3	NA	Dead 45.3
080	Haemophilia A	0.16	24.7	NA	45.8	NA	Alive 52.6
103	Haemophilia B	0.01	23.0	NA	40.7	NA	Dead 41.5
131	Haemophilia A	0.01	17.4	29.0	38.3	36.6	Dead 38.3
121	Haemophilia A	0.01	5.8	16.5	27.0	NA	Dead 28.7
054	Haemophilia A	0.01	3.6	14.7	25.4	25.4	Transplant 26.4
032	Haemophilia A	0.01	1.4	12.6	8.4	NA	Alive 24.3

years after HCV infection at least 19% of cohort patients developed cirrhosis and 9% developed liver failure

*Hepatocellular carcinoma*

Two patients developed hepatocellular carcinoma (HCC). The first patient was shown by liver biopsy to have had cirrhosis 13 years prior to the identification of HCC. As no metastases were present he underwent liver transplantation and is alive and well 5 years later. The second patient received only a single batch of non-virally inactivated FVIII concentrate. He was HIV negative but presented 11 years later with end-stage liver failure. Limited autopsy confirmed the presence of HCC.

*Factors influencing disease progression*

Multivariate analysis using Cox's proportional hazards model was used to analyse the effect of severity of haemophilia, HIV status and age at infection with HCV on the development

of cirrhosis and liver failure. This analysis allows for a change in the baseline incidence over time, i.e. the observed increasing risk after > 15 years. In a model including age (in years), severity of haemophilia (mild/moderate/severe) and HIV infection (positive or negative), severity of haemophilia appeared not to be associated with the risk of development of either cirrhosis or liver failure (Table IV). Patients who were HIV positive had a 3.9-fold increased incidence of liver cirrhosis (CI 95% 1.4–10.8) compared to those who remained HIV negative. The risk of cirrhosis appeared to be higher for those who were infected at an older age, with an average of a 5% higher risk for each year older a patient was when infected. Because of the scarcity of data, it was not possible to assess all age classes in the multivariate model and so determine whether this average is true over all age groups. In the model with only the age classes, we did not find a steadily increased risk with age at the time of infection, but a constant risk was found for those infected before the age of 20 years and a

Table III The incidence and 95% confidence intervals of cirrhosis and liver failure after HCV infection shown per 1000 person years

Time since HCV infection (yr)	Cirrhosis		Liver failure	
	Incidence	CI 95	Incidence	CI 95
0–4	2.91	0.25–8.48	0	0.00–4.35
5–9	7.55	2.31–15.81	4.41	0.79–10.99
10–14	3.74	0.32–10.89	3.64	0.31–10.60
15+	15.56	7.27–26.95	5.9	1.48–13.28
All	7.52	4.46–11.36	3.47	1.54–6.16

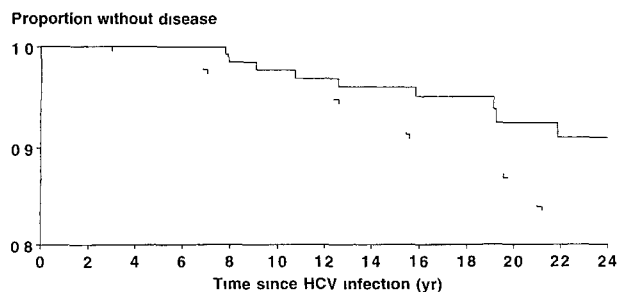


Fig 1 Kaplan Meier analysis showing cumulative incidence of cirrhosis (broken line) and liver failure (solid line) following HCV infection in the 138 cohort patients

Table IV. Multivariate modelling results.

	Cirrhosis as endpoint		Liver failure as endpoint	
	Hazards ratio	CI 95	Hazards ratio	CI 95
Univariate analysis				
Severity of haemophilia				
Mild	1.0		1.0	
Moderate	0.76	0.16–3.67	1.82	0.30–10.97
Severe	0.77	0.29–2.04	0.75	0.17–3.4
Grouped linear	0.88	0.54–1.44	0.85	0.42–1.73
HIV status				
Negative	1.0		1.0	
Positive	2.36	0.96–5.81	2.10	0.56–7.82
Age at infection (yr)				
0–4	1.0		1.0	
5–9	0.50	0.045–5.51		
10–19	0.36	0.032–3.93		
20–29	2.23	0.43–11.49		
30–39	1.94	0.27–13.82		
40+	5.42	1.15–25.56		
Grouped linear	1.64	1.21–2.22	2.14	1.27–3.60
Multivariate analysis				
Severity of haemophilia	0.80	0.46–1.41	0.83	0.37–1.83
HIV status	3.88	1.40–10.76	4.18	0.94–18.55
Age at infection	1.80	1.28–2.54	2.43	1.36–4.32
Model with age in years				
Severity of haemophilia	0.85	0.48–1.53	0.96	0.41–2.21
HIV	3.92	1.42–10.85	4.21	0.96–18.41
Age at infection	1.05	1.03–1.08	1.08	1.04–1.13

higher increasing risk identified for those infected after age 20 (although the numbers in each age group were too small to allow formal tests of significance). In this univariate analysis, the risk was highest for those who were 40 years and older when infected: they had a 5.4-fold higher incidence of cirrhosis than those who were 0–4 years old when infected (CI 95 1.2–25.6).

The results for liver failure were essentially similar: severity of haemophilia had no effect on the development of liver failure, neither in univariate analysis nor when adjusted for HIV infection and age at HIV infection, whereas the risk was increased 4.2-fold for the HIV-positive patients (CI 95 1.4–4.3) and also increased by age (hazards ratio 1.08, CI 95 1.04–1.13), i.e. an 8% higher risk for developing liver failure during follow-up for each year older a patient was at the time of HCV infection.

## DISCUSSION

We found that 83.2% of patients had abnormal transaminases consistent with the diagnosis of chronic HCV. This figure is similar to that reported by Cederbaum *et al* (1982) from the U.S.A. (85%) and also by Telfer *et al* (1994) (83.5%). Cederbaum *et al* (1982) used the same method of defining abnormal ALT as we did (i.e. on the basis of the last three levels), but as it was carried out prior to the HCV identification

the patients were not preselected on the basis of HCV antibody. Telfer *et al* (1994) selected their patients in an identical manner to ours but based their figures on the ALT pattern over the last 5 years. It is unclear how many of the patients with normal ALT have cleared the HCV virus and are now immune. The literature suggests that HCV becomes chronic in only 50% of non-haemophiliac patients, a figure much lower than the > 80% seen in haemophiliacs. Our data suggest that even patients with normal ALT can have chronic HCV, as shown by the fact that 11/15 (73%) patients tested were found to be viraemic; 2/5 of these patients had cirrhosis on liver biopsy. We have no liver histology from the small number of patients who have normal enzymes and are HCV PCR negative, so it is not possible to conclude that any haemophiliac has cleared the HCV virus.

Evidence of past infection with hepatitis A was found in 37.2% of our patients, a figure very similar to that found in the general U.K. population, suggesting that this virus was not transmitted to any significant degree by non-virally inactivated concentrates. Despite the fact that 48.1% of patients have had infection with hepatitis B at some time, only three (2.2%) patients remain HBsAg positive, a figure similar to other U.K. series (Telfer *et al*, 1994); this confirms the very minor role that chronic hepatitis B has in the development of chronic liver disease in haemophiliacs. 26.1% of this cohort were HIV positive, a figure lower

than the two recent series reporting accelerated liver disease in HIV-positive haemophiliacs. In the Telfer cohort, 40.4% of patients were co-infected with HIV/HCV (Telfer *et al*, 1994), whereas Eyster *et al* (1994) found that 62.8% of the patients were co-infected with both HIV and HCV. The difference between our co-infection figures and those of Telfer and Eyster are important in assessing the natural history of the cohort as a whole.

In our cohort, survival analysis has shown that after 22 years at least 19% of the patients have cirrhosis and 9% liver failure, providing evidence that liver disease is now becoming a major cause of morbidity and mortality in haemophilia. The incidence of cirrhosis increases with time after HCV infection to 15.56 per 1000 person-years, 15 years after infection. Within the time period of follow-up of our cohort no significant increase in the incidence of liver failure with time was seen. Our interpretation of this is that the risk of cirrhosis is present from early infection onwards, but remains quite low, and fairly constant, until around 15 years post infection, after which the risk increases dramatically. The development of liver failure lags 5–10 years after cirrhosis, so the increase is much less clear since follow-up is not yet long enough. If we are correct, this finding has important implications for the haemophilia community who were infected with HCV around 20 years ago and would only now be expected to start presenting with liver failure in significant numbers.

Co-infection with the HIV virus was the most important factor contributing to the development of cirrhosis and liver failure. This is consistent with the findings reported by Eyster *et al* (1993) in Pennsylvania and Telfer *et al* (1994) in London. It is important to appreciate, however, that significant HCV morbidity and mortality occurs in HIV-negative patients; indeed in our cohort half of the patients with documented cirrhosis or liver failure were HIV negative. The possibility of more rapid progression of liver disease in HIV co-infected patients was first raised by Martin *et al* (1989), who observed that progression of NANB hepatitis to liver failure in three HIV-positive patients occurred within 3 years of the hepatitis infection through blood transfusion. It is unclear why liver disease progresses more rapidly in HIV-positive patients. Patients with HIV infection have higher circulating HCV RNA levels and it has been suggested that concurrent opportunistic infections in these patients could precipitate liver failure in an already cirrhotic liver (Telfer *et al*, 1994). Similar accelerated liver disease in immunocompromised patients has been observed in patients with combined immunodeficiency who were infected with HCV through contaminated intravenous immunoglobulin (Bjoro *et al*, 1994) and in patients who have had liver transplants for HCV where the immunosuppression given to prevent graft rejection appears to contribute to the accelerated HCV that invariably infects the new liver (Villa *et al*, 1995).

We have identified age as an important variable in the rate of progression of the liver disease. Both the age of the patient at the time of infection and the time since HCV infection were independently associated with disease progression. A similar observation was reported in non-haemophiliacs by Yano *et al*

(1993) who performed serial liver biopsies in Japanese patients who acquired their HCV through blood transfusion. Although it is easy to see why the period of time since infection is important in disease progression of a chronic disease, it is more difficult to explain why the age at the time of infection is important. A similar acceleration in disease progression in older patients has already been reported for HIV infection in haemophiliacs (Darby *et al*, 1990).

Two of our cohort patients developed hepatocellular carcinoma. This complication of HCV in haemophiliacs was first reported by Colombo *et al* (1991), who, in a multicentre study, found HCC to be 30 times greater than expected. Recently, a similar increase was reported from the U.K. (Preston *et al*, 1995a). Since screening with hepatic ultrasound and alpha fetoprotein estimation offers the possibility of early HCC diagnosis and as liver transplantation offers the possibility of 'cure' in those diagnosed early, it should be considered in the follow-up of all HCV-positive haemophiliacs.

Our study is strengthened by the long period of follow-up and the large number of patients and liver biopsies performed in this cohort. Any bias due to back-extrapolation of the follow-up period, if present, will be small and will not affect our conclusions: first we observed an increasing risk with time since infection, which cannot be explained by cirrhotic deaths occurring in the early years following infection of patients who were never part of our cohort (there were very few deaths from cirrhosis in haemophilia patients in the U.K. before 1980); second, from the pathogenesis of hepatitis and cirrhosis, an increasing risk over time is plausible.

It is unlikely that many patients were infected with HCV from unscreened blood, fresh frozen plasma and cryoprecipitate before the introduction of concentrates; the incidence of confirmed HCV infections in blood donors of our region is 0.05% (V. James, personal communication).

The 19 patients found to have cirrhosis is likely to be a great underestimate since some non-biopsied patients are likely to have asymptomatic cirrhosis. Furthermore, patients biopsied some years ago are likely to have progressed to asymptomatic cirrhosis.

Although alcohol may accelerate progression of chronic HCV-related liver disease, only 15.3% of our cohort admitted to be drinking more than 20 units of alcohol per week, and none of the biopsies contained sufficient Mallory's hyalin to suggest that alcohol was a more likely cause for the liver injury.

We conclude that most haemophiliacs treated with non-virally inactivated concentrates have biochemical and histological evidence for chronic hepatitis. Within 22 years of infection at least 19% of patients have cirrhosis and 9% have developed liver failure. In addition to an accelerating effect of HIV on HCV-related liver disease, we have also demonstrated that progression is influenced by increasing age at the time and the interval since HCV infection. These are the same factors that mitigate against interferon response and therefore in the context of chronic liver disease in haemophilia there is an urgent need to explore new therapeutic modalities.

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