Clin Exp Immunol 1997; **110**:4–8

Clinical outcome of hypogammaglobulinaemic patients following outbreak of acute hepatitis C: 2 year follow up

J. M. L. CHRISTIE, C. J. HEALEY, J. WATSON, V. S. WONG, M. DUDDRIDGE, N. SNOWDEN, W. M. C. ROSENBERG, K. A. FLEMING, H. CHAPEL & R. W. G. CHAPMAN *Department of Gastroenterology, Nuffield Department of Pathology and Bacteriology and Nuffield Department of Clinical Medicine, John Radcliffe Hospital, Oxford, UK*

(Accepted for publication 5 July 1997)

SUMMARY

In 1994, an outbreak of hepatitis C virus (HCV) infection, genotype 1a, occurred in 30 hypogammaglobulinaemic patients in the UK from one batch of contaminated anti-HCV screened intravenous immunoglobulin. This study aimed to study prospectively the outcome of HCV in hypogammaglobulinaemic patients, and to assess the response to early treatment with interferon-alpha, 6 million units three times weekly for 6 months. Data were collected using standardized questionnaires. Five patients with secondary hypogammaglobulinaemia due to lymphoid malignancy were not treated and all have died of their primary malignancy. Of 25 patients with primary hypogammaglobulinaemia, one resolved HCV infection before treatment, 17 commenced on treatment, and seven declined or treatment was contra-indicated. Thirteen of 17 patients completed therapy and seven (54%) have a sustained response (normal transaminases, negative serum HCV RNA) at 6 and 12 months after treatment. Two of the 12 patients with primary hypogammaglobulinaemia, who were not treated or failed to complete treatment, have cleared the virus. Liver biopsy was performed in patients not clearing HCV and was abnormal in all. Four patients developed liver failure within 2 years, of whom three have died and one has been successfully transplanted. In conclusion, HCV can cause rapid severe liver disease in hypogammaglobulinaemic patients. Early treatment with high-dose interferon-alpha results in a high clearance of HCV.

Keywords hepatitis c virus immunologic deficiency syndromes immunoglobulins interferons

INTRODUCTION

In February 1994, Baxter Healthcare Ltd withdrew Gammagard, an intravenous preparation of human immunoglobulin (IvIg) because of case reports of acute hepatitis C infection associated with its use [1]. Transmission had occurred despite the introduction of anti-HCV screening of each plasma donation contributing to the large plasma pools (approx. 15 000 donations from approx. 2000 donors) from which the product was derived. Since then over 200 suspected cases have been reported worldwide, associated with several different batches of the product which have been shown to contain HCV RNA [2]. Within the UK, only one batch was suspected of transmission and this was subsequently proven by both clinical and molecular epidemiology [3]. Accurate documentation of batch numbers by both the suppliers and prescribers enabled the identification and subsequent follow up of all exposed individuals. Thirty hypogammaglobulinaemic patients were shown to have acute HCV infection from 36 patients known to have received the contaminated batch.

Experience of HCV in hypogammaglobulinaemic patients infected following infusion of IvIg suggested that the liver disease could be rapidly progressive and responded poorly to interferon-alpha (IFN-α) [4–8]. These small studies of IFN-α treatment were in patients with chronic infection of undefined length and with unknown or mixed genotypes of HCV. However, the UK Gammagard outbreak provides an unique opportunity to study the rate of progression of HCV in hypogammaglobulinaemic patients with known onset of infection and a single genotype (genotype 1a) as well as their response to therapy. We chose therapy in the acute phase with high dose IFN-α as greater efficacy had been suggested with higher doses [9,10] and early treatment [11,12].

Correspondence: Dr John Christie, Department of Gastroenterology, John Radcliffe Hospital, Oxford OX3 9DU, UK.

PATIENTS AND METHODS

Patients

Thirty-six UK patients received treatment with the HCV-contaminated

© 1997 Blackwell Science

batch of IvIg (93F21AB11B: Gammagard), 30 of whom were shown to have developed acute infection with HCV. The clinical details of these patients have been reported previously [3]. All the infected patients in the UK exposed to the batch were followed up using standardized questionnaires. These patients came from throughout the UK and were under the supervision of their individual regional immunology centres. The indication for gammaglobulin therapy can be categorized into two main groups: patients with primary antibody deficiency (16 common variable immunodeficiency, seven IgG subclass deficiency, one X-linked agammaglobulinaemia, one drug-induced hypogammaglobulinaemia) and patients with immune paresis secondary to malignancy (three chronic lymphocytic leukaemia (CLL), two myeloma). The diagnosis of primary hypogammaglobulinaemia was made using standard criteria [13].

Virological investigation

Twenty-eight of 30 patients were repeatedly positive for HCV RNA by reverse transcriptase polymerase chain reaction (RT-PCR) after exposure to the batch. The mean length of time from exposure to the batch and the first positive HCV PCR test was 37·5 days (range 7–71 days) with 92·3% of patients being positive on the first test. Fourteen of these viral isolates underwent sequence analysis revealing identical isolates of HCV genotype 1a as we have previously reported. The remaining two patients developed abnormal liver function tests and seroconverted to anti-HCV positive.

Treatment protocol

IFN-α therapy was considered for all patients with proven HCV infection. In view of the previously reported severity of HCV infection amongst patients with primary antibody deficiency and the iatrogenic nature of transmission, the UK Gammagard Users Group considered that it would be unethical to withhold interferon therapy from the patients with primary hypogammaglobulinaemia, although in seven treatment was contra-indicated or declined. Therapy was recommended at 6 million units of IFN-α, three times weekly, subcutaneously for a planned period of 6 months according to a standard protocol; the dose could be reduced by the supervising physician if clinically indicated. Response was measured by both improvement in liver enzyme levels and clearance of circulating HCV RNA detected by RT-PCR. A sustained response was defined as normalization of liver transaminases and absence of HCV RNA from the serum at both 6 and 12 months after therapy. Treatment and follow-up data were collected centrally by the use of serial data sheets. Patients with hypogammaglobulinaemia secondary to malignancy were not offered therapy.

RESULTS

Clinical follow up

Thirty patients with acute HCV infection were followed and their initial outcomes are summarized in Fig 1. The five patients with malignancy (three CLL, two myeloma) were considered inappropriate for therapy with IFN-α in view of their underlying condition. One patient, an infrequent attendee, had abnormal liver function documented by his primary-care physician but subsequently his liver function returned to normal and he became anti-HCV positive; he has never been found to be positive for HCV RNA and is therefore considered to have resolved the HCV infection acutely.

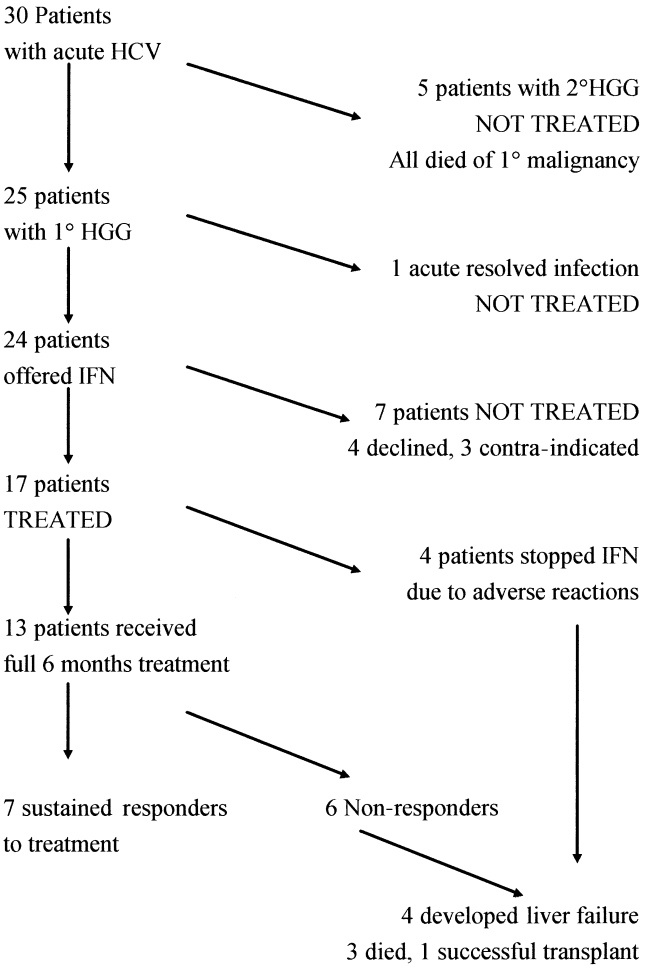

Fig. 1. Summary of initial outcome of HCV infection amongst hypogammaglobulinaemic patients in the UK Gammagard Outbreak. HGG, hypogammaglobulinaemia; IFN, interferon-alpha.

The remaining 24 patients were considered for therapy with IFN-α of which 17 patients started treatment. Seven patients did not receive interferon; four declined therapy and therapy was contra-indicated in three, in view of other severe medical conditions (severe depression, granulomatous liver disease, chronic pulmonary suppuration).

Treatment group

Seventeen patients with primary antibody deficiency were commenced on treatment with interferon (13 with common variable immunodeficiency, three with IgG deficiency and one with X-linked agammaglobulinaemia). The mean age of the treated group was 40·4 years, with a male : female ratio of 10 : 7. The mean time between exposure to the infected batch and commencement of treatment was 4·3 months (range 1–9 months). The majority of patients (14/17) started treatment within 6 months of inoculation. Fourteen patients commenced therapy at full dose and three started at reduced dose. Four patients withdrew from treatment before the end of the 6 months (including all three who started at a reduced dose). Reasons for withdrawal included severe lethargy (two patients), epistaxis/thrombocytopaenia (one patient) and depression (one patient). Thirteen patients completed therapy with interferon, 11 achieving the full cumulative dose and two patients

received 80% and 60% of the full dose each (although five patients required a reduction in the dose, three of these patients received longer than 6 months therapy and therefore received the full cumulative dose).

Liver enzymes returned quickly (within 1 month) to pre-treatment levels in 11/13 patients completing treatment with IFN-α. Rapid biochemical (within 1 month) and viraemic relapse was seen in six patients following cessation of treatment. Liver enzymes have remained normal in seven patients, all of whom have shown a sustained response with a persistently negative HCV PCR for greater than 1 year following treatment with IFN-α. This represents a sustained response rate of 41% of those commenced on interferon or 54% of patients who completed therapy.

There was no difference between the age of patients who had a sustained response to interferon and patients unresponsive to treatment. We also found no correlation of IgG, IgA or IgM levels with response to treatment.

Untreated group

Thirteen patients received no treatment; five with secondary hypogammaglobulinaemia due to lymphoid malignancy and eight with primary hypogammaglobulinaemia.

The five patients with secondary hypogammaglobulinaemia died of their malignancy within the 2-year follow-up period, without evidence of hepatitis contributing to their deaths. One of these patients never became PCR positive but seroconverted within 4 months of infection and had continuing biochemical evidence of hepatitis.

Of the eight untreated patients with primary hypogammaglobulinaemia, two are HCV PCR negative. One of these patients cleared HCV before treatment could be commenced (considered acute clearance of HCV infection—see above), one other patient, who refused treatment, became HCV PCR negative after 6 months; both patients remain well. One additional patient has died of unrelated causes. Five patients remain HCV PCR positive. In total, two out of 13 patients not treated with interferon have appeared to clear HCV without interferon treatment.

Disease progression

Within 2 years of exposure to HCV infection, three patients developed cirrhosis, of whom one died before liver transplantation, one died shortly after liver transplantation and one remains alive following transplantation. Two of these patients had additional immune suppression; one was receiving prednisolone for

Table 1. Results of histology

Patient no.	Time from exposure to biopsy (months)	Clinical information at time of biopsy	Description	Knodells score	New international index (Ishak *et al*.) [19]	
					Grade	Stage
5	12	PCR-negative	Minimal hepatitis No fibrosis	3	3	0
9	13	Post IFN. PCR-positive	Chronic hepatitis, stage 1 fibrosis	3	2	1
10	14	Post IFN. PCR-positive	Mild chronic active hepatitis	NA		
10	19	Post IFN and ribavirin	Severe chronic active hepatitis Early cirrhosis	NA		
10	28	Prior to transplantation	Cirrhosis	NA		
11	12	Post IFN. PCR-positive	Chronic active hepatitis, stage 1 fibrosis	10	7	2
11	24	on Tx with IFN and ribavirin	Chronic hepatitis Improved from previous biopsy	7	NA	NA
11	29	Post IFN and ribavirin	Severe chronic active hepatitis, stage 3 fibrosis	15	NA	NA
12	14	Post IFN. PCR-positive	Chronic active hepatitis Cirrhosis	14	9	5
13	13	Post IFN. PCR-positive	Mild chronic hepatitis, stage 1 fibrosis	4	4	1
14	13	IFN discontinued. PCR-positive	Chronic hepatitis, stage 3 fibrosis	15	12	4
14	20	During transplantation assessment	Cirrhosis	NA		
17	9	Post IFN. PCR-positive	Moderately severe chronic active hepatitis	11	8	3
18	30	Not treated with IFN (granulomatous liver dx Δ1991)	Severe chronic active hepatitis, stage 3 fibrosis	12		

autoimmune haemolytic anaemia and the other was 28/40 weeks pregnant at the time of exposure. A further patient who died of bronchopneumonia secondary to long-standing bronchiectasis and cor pulmonale, was also suffering from sub-acute liver failure (bilirubin > 500 IU/*l* and prothrombin > 30 s). None of these four patients received the full cumulative dose of interferon due to significant side-effects of treatment (two discontinued treatment, two received reduced dosage). This represents a 17% rate of progression to end-stage liver failure within 24 months amongst the patients with primary immunodeficiency.

Amongst the patients who have relapsed following their treatment there is evidence of morbidity, and three patients have started a second course of therapy of which two have commenced on ribavirin and interferon.

Histology

Liver histology was available from seven of 11 patients who relapsed after full therapy or failed to tolerate IFN-α, in one patient who cleared the virus and in one patient who was not treated—a total of 14 biopsies from nine patients. The histological findings are summarized in Table 1, and were abnormal in all. In one patient, liver histology was available from three time points. A first biopsy was taken when he presented in 1988 with autoimmune haemolytic anaemia, and was normal. A second biopsy taken 12 months after exposure to HCV during a laproscopic cholecystectomy for cholelithiasis, shows chronic hepatitis with interface hepatitis and a Knodells histological activity index (HAI) score of 14. A final biopsy taken 18 months following exposure to IvIg as part of liver transplant assessment showed cirrhosis. Previous exposure to HCV was conjectured, as this patient had received a number of transfusions of packed erythrocytes (before the introduction of anti-HCV screening) for haemolytic anaemia. However, biochemical evidence of hepatitis developed only after his exposure to the contaminated IvIg batch and the HCV isolate detected was genotype 1a and identical in sequence analysis to others from the rest of the outbreak.

DISCUSSION

In four out of 25 patients with primary antibody deficiency we have observed rapid progression of HCV infection, with end-stage liver disease occurring within a period of 18 months. Such rapid progression to cirrhosis is rarely seen in HCV-related liver disease; this outcome is highly unusual when compared with post-transfusion HCV in immunocompetent patients [4]. Liver biopsy results also show evidence of rapid progression of fibrosis in a further two patients, who have not cleared the virus, over a 2-year period. One of these patients was known to have pre-existing liver disease (granulomatous liver disease) and the other had no previously known liver disease. Thus overall in our group we have evidence of rapid progression of liver fibrosis in six out of 25 patients (24%).

In contrast to some of the other reports of patients with HCV and hypogammaglobulinaemia, some of the patients have done well. Two patients have spontaneously cleared this virus without any treatment. Of the remaining 10 patients who have not cleared the virus but who have not had rapidly progressive liver disease, two have had liver biopsies showing stage 1 fibrosis; one of these patients remains well and the other has died of unrelated causes. Two further patients have died of unrelated causes. The remaining six patients are asymptomatic, although have not been assessed by liver biopsy.

Seven patients (54%) treated with interferon for more than 3 months have shown a sustained response with normal liver function tests and negative RT-PCR 2 years after treatment. Overall the sustained response to interferon compares favourably to the 20% sustained response rate seen in other studies. This may be due to the prompt treatment and high-dose regimen that the patients received.

One alternative to acute treatment with IFN-α was to wait and treat only when the disease had become chronic, as a small proportion of patients will spontaneously clear HCV. Indeed we have found that two patients with antibody deficiency cleared HCV without treatment. However, Bjoro *et al.*'s experience with similar patients showed very poor efficacy for IFN-α in established chronic infection [8]. This may be due to the length of infection prior to treatment, different genotypes or mixed infections. The need for early treatment is highlighted by the suggestion that liver transplantation for end-stage liver disease in hypogammaglobulinaemia has a poor outcome [15]. However, our results show a high clearance rate of HCV (7/13 = 54%) when hypogammaglobulinaemic patients receive and tolerate high-dose interferon therapy within 9 months of infection.

Previous published reports suggest that the clinical outcome of HCV in primary antibody deficiency is variable. Possible explanations for these differences involve host factors including coexisting morbidity and viral factors. Pre-existing conditions may partly explain the rapid progression as exemplified by two patients in our group. One patient who died of liver failure also suffered from haemolytic anaemia, requiring maintenance corticosteroid therapy, another severely affected patient was pregnant at the time of exposure; both these factors would lead to increased immunosuppression. Nonetheless, steroid treatment alone or pregnancy has not been previously reported to lead to such rapid progression of HCV liver disease.

Underlying liver disease may also contribute. Patients with CVID are recognized to have an increased risk of liver pathology, but the literature is limited to a few case reports of granulomatous change similar to that seen in sarcoidosis [16]. However the four patients who progressed to end-stage liver disease had no evidence of previous liver abnormality, as extensively documented by serial liver-function tests performed prior to exposure.

Viral factors could also aggravate or attenuate the liver disease. There are known differences between viral genotypes in the severity of disease and response to interferon therapy. Our patients were known to be infected with one single genotype 1a. Although genotype 1 infections have been suggested to be more severe than other genotypes [17], the degree of progression seen in some patients is far greater than could be explained by this factor alone.

The contribution of other viruses should also be considered. Recently a further flavivirus HGV (HGBV-C), sharing limited homology has been identified [18] and has been suggested to be another potential co-factor in patients receiving blood products. This has not been found to be the case in this cohort with the incidence of HGV infection being less than 10% and not found in any of the severe cases (Peter Simmonds, personal communication).

All blood products, especially those produced from pooled donations, are potential sources of infection. In order to be aware of such outbreaks and to enable accurate diagnosis and follow up, it is important to document the products used and their batch numbers together with careful clinical and biochemical monitoring in all recipients. It is also important that patients receive only one product and that the brand is only changed for medical reasons. We believe our study confirms the severe potential nature of HCV

infection in some patients with hypogammaglobulinaemia, although it is difficult to predict who will do badly. In the unfortunate event of an HCV outbreak, early diagnosis is important as prompt treatment with high-dose interferon benefits patients.

ACKNOWLEDGMENTS

The UK Gammagard users group wish to acknowledge the help and assistance of Baxter Healthcare Limited and all the following centres for the collection of the clinical data: Professor M. Bassendine and Dr G. Spickett, Newcastle; Dr R. Powell and Dr S. Ryder, Queens Medical Centre, Nottingham; Dr M. Haeney, Hope Hospital Salford; Dr C. Clarke, Selly Oak Hospital, Birmingham; Dr G. Alexander, University of Cambridge Clinical School of Medicine; and Dr R. Barry and Dr T. Wallington, Bristol.

REFERENCES

1 Outbreak of hepatitis C associated with intravenous immunoglobulin administration—United States, October 1993–June 1994. MMWR 1994; **43**:505–9.

2 Yu MW, Mason BL, Guo ZP, Tankersley DL, Nedjar S, Mitchell FD, Biswas RM. Hepatitis C transmission associated with intravenous immunoglobulins. Lancet 1995; **345**:1173–4.

3 Healey CJ, Sabharwal NK, Daub J, Davidson F, Yap PL, Fleming KA, Chapman RWG, Simmonds P, Chapel H. Outbreak of acute hepatitis C following the use of anti-hepatitis C virus screened intravenous immunoglobulin therapy. Gastroenterology 1996; **110**:1120–6.

4 Webster ADB, Lever AML. Non-A non-B hepatitis after intravenous gammaglobulin [letter]. Lancet 1986; **327**:332.

5 Weiland O, Mattsson L, Glaumann H. Non-A, non-B hepatitis after intravenous gammaglobulin [letter]. Lancet 1986; **327**:976–7.

6 Thomson BJ, Doran M. Lever AM, Webster AD. Alpha-interferon therapy for non-A, non-B hepatitis transmitted by gammaglobulin replacement therapy. Lancet 1987; **329**:539–41.

7 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**:107–11.

8 Bjoro MD, Froland SS, Yun Z, Samdal HH, Haaland MD. Hepatitis C infection in patients with primary hypogammaglobulinaemia after treatment with contaminated immune globulin. N Engl Med 1994; **331**:1607–11.

9 Alberti A, Chemello L, Bonetti P, Casarin C, Diodati G, Cavalletto D, Frezza M, Donada C, Belussi F, Casarin P, Pozzato *et al*. Treatment with interferons of community-acquired chronic hepatitis and cirrhosis type C. J Hepatol 1993;**17**(Suppl.3):S123–6.

10 Davis GL. Prediction of response to interferon treatment of chronic hepatitis C. J Hepatol 1994; **21**:1–3.

11 Viladomiu L, Genesca J, Estaban JI, Allende H, Gonzalez A, Lopez-Talavera JC, Esteban R, Guardia J. Interferon-α in acute posttransfusion hepatitis C: a randomised controlled trial. Hepatology 1992; **15**:767–9.

12 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 transfusion-associated hepatitis C. Hepatology 1994; **19**:19–22.

13 Chapel HM. Consensus in diagnosis and management of primary antibody deficiencies. Br Med J 1994; **308**:581.

14 Seef LB, Buskell-Bales Z, Wright EC, Durako SJ, Alter, HJ, Iber FL, *et al*. Long term mortality after transfusion associated non-A, non-B hepatitis. N Engl J Med 1992; **327**:1906–11.

15 Smith MSH, Webster DB, Dhillon AP, Dusheiko G, Boulton R, Savage K, Rolles K, Burroughs AK. Orthotopic liver transplantation for chronic hepatitis in two patients with common variable immunodeficiency. Gastroenterology 1995; **108**:879–84.

16 Leen CLS, Bath JCJL, Brettle RP, Yap PL. Sarcoidosis and primary hypogammaglobulinaemia: a report of two cases and a review of the literature. Sarcoidosis 1985; **2**:91–5.

17 Dusheiko G, Schmilovitz H, Brown D, McOmish F, Yap PL, Sherlock S, McIntyre N, Simmonds P. Hepatitis C virus genotypes: an investigation of type-specific differences in geographic origin and disease. Hepatology 1994; **19**:13–18.

18 Simons JN, Leary TP, Dawson GJ, Pitol-Matias TJ, Muerhoff AS Schlauder GG, Desai SM, Mushahwar IK. Isolation of novel virus-like sequences associated with human hepatitis. Nature Med 1995; **1**:564–8.

19 Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F *et al*. Histological grading and staging of chronic hepatitis. J Hepatol 1995; **22**:696–9.