

Early experience with chronic hepatitis C in Northern Ireland: epidemiology and response to monotherapy

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SUMMARY

Chronic hepatitis C virus (HCV) infection has become a major health problem affecting an estimated 170 million people worldwide. The epidemiology of HCV and its response to treatment in Northern Ireland has not been described before.

Our aims were to determine the epidemiology, histological stage, suitability for treatment and response to treatment in patients with hepatitis C presenting to one clinic in Northern Ireland. All patients were prospectively recruited with hepatitis C attending the Liver Clinic, Royal Victoria Hospital during the period December 1992 to June 1997.

Sixty patients (33 male, mean age 44 years, range 19-84 years) who tested anti-HCV antibody positive were identified. The predominant genotypes were 1b (33%), 3a (28%) and 1a (26%). Most patients (78%) were asymptomatic at the time of detection and only four (7%) gave a history of jaundice. The most common modes of transmission were i.v. drug use in 30 (50%) and blood products in 20 (33%) patients. Forty-eight (86%) of the 56 patients tested were PCR positive for HCV RNA. Fifty-one patients (85%) underwent liver biopsy of whom 13 had cirrhosis (22% of original group). Twenty-nine patients were suitable for treatment, but three declined treatment and only 26 (43%) started interferon-alpha. During treatment 17 (65%) patients became PCR negative and eight (31%) remained PCR negative 12 months after completion of therapy. Liver histology was assessed before and after interferon treatment in 17 patients and showed no change in total necroinflammatory scores ($p=0.1$) or staging of architectural change ($p=0.55$).

Conclusions: The epidemiology and response to therapy of HCV in Northern Ireland appear comparable to elsewhere in the UK. Only a minority of anti-HCV positive non-haemophilic patients progress to have interferon therapy suggesting that the cost of treating chronic HCV may not be as great as initially thought.

INTRODUCTION

The hepatitis C virus (HCV) results in chronic hepatitis C (CHC) in up to 85% of those acutely infected.¹ Chronic HCV infection has become a major health issue throughout the world affecting an estimated 170 million people.² Up to one third of those with CHC will develop cirrhosis, and end-stage liver disease due to CHC is now the leading indication for liver transplantation worldwide.³ The goal of therapy is obviously to prevent progression to end-stage liver disease with its consequences. Monotherapy with interferon alpha was the mainstay of treatment for CHC from the virus was first identified in 1989 until the late 1990's. Given the scale of the

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HCV problem, the cost of treating most HCV patients is potentially enormous. However not all chronic HCV patients may be suitable for treatment and some have fairly indolent disease that does not require therapy.

Despite over a decade of experience with HCV, debate continues regarding whom to treat and how. Studies have shown that a number of factors can influence response to therapy such as viral load and viral genotype.⁴ There are six main HCV genotypes and genotype 1 is associated with a worse response to interferon therapy. The prevalence of genotype 1 varies throughout the world and its prevalence in Northern Ireland is unknown. Northern Ireland is thought to have a lower incidence of i.v. drug abuse (one of the main risk factors for HCV) than elsewhere in the United Kingdom but the epidemiology of HCV in Northern Ireland has not previously been described. Variations in factors such as genotype prevalence could translate into different treatment response rates in Northern Ireland compared to elsewhere.

Chronic HCV patients were first treated with interferon in Northern Ireland in 1992 and patients were treated with the same monotherapy protocol until 1997 when the NIH Consensus Statement on Management of Hepatitis C was published leading to a change in treatment protocols.⁶ The aims of this study were twofold: To prospectively recruit all non-haemophiliac chronic HCV patients presenting to the largest hepatology clinic in Northern Ireland from 1992 until 1997 and to describe their demographic details; and secondly, using clearly defined criteria, to determine the proportion of such patients who required treatment and to describe their histological and biochemical responses.

PATIENTS AND METHODS

All non-haemophiliac patients attending the Hepatology Clinic at the Royal Victoria Hospital, Belfast who were found to be anti-HCV positive during the period December 1992 to June 1997 were prospectively recruited. Preliminary assessment involved blood testing for liver biochemistry, anti-HCV antibody, HCV RNA testing by polymerase chain reaction (PCR) and HCV genotyping. Liver biopsy was offered to all patients who had a positive PCR for HCV-RNA or had abnormal LFTs. Patients who were PCR positive for HCV-RNA who had evidence of interface or intralobular hepatitis or cirrhosis on

liver biopsy and were medically fit to undergo treatment were offered interferon alpha therapy. Those patients who had decompensated cirrhosis, human immunodeficiency virus (HIV) infection, severe co-morbidity, pregnancy, continued intravenous drug abuse, other causes of chronic liver disease or who were PCR negative were excluded from treatment.

Interferon alpha 2a was given as a starting dose of 3 million units (MU) subcutaneously thrice weekly for 1 month, then 4 MU thrice weekly for 1 month and finally up to 5 MU thrice weekly for 6 months with monthly monitoring of LFTs, FBP and HCV-RNA PCR. Patients who had difficulty with side-effects or a low platelet count due to interferon were maintained for 6 months on the maximum dose tolerated.

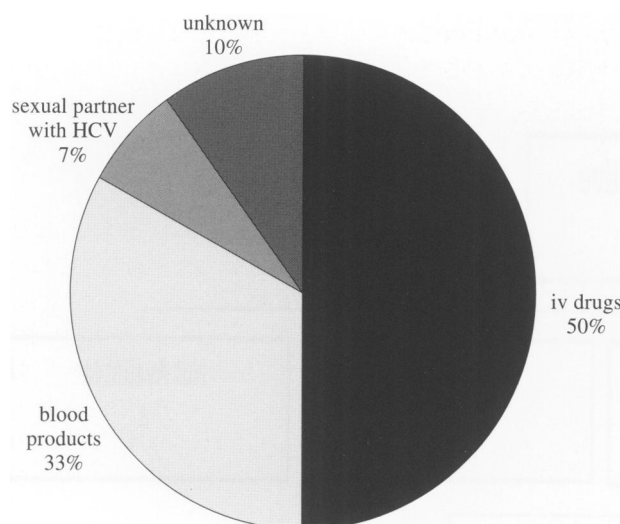
On completion of therapy, LFTs and PCR were monitored every 3 months in those who had become PCR negative during treatment and a repeat liver biopsy was offered. Biopsies were independently scored by two pathologists who were blinded to the timing of each biopsy with relation to treatment. Each biopsy was scored for necroinflammation (0-18) and fibrosis (0-6) in accordance with the previously published modified Knodell Histology Activity Index for grading and staging of chronic hepatitis (Ishak *et al*, J Hepatol, 1995).

Treatment response was defined as clearance of virus from the blood (PCR negative) and normalisation of ALT at completion of therapy and sustained viral response as the maintenance of this response at 6 months after completion of therapy.⁷

RESULTS

Sixty patients were recruited (33 male, mean age 44 years, age range 19-84 years). The most common genotypes were 1b (33%), 3a (28%) and 1a (26%). Most patients (47 (78%)) had minimal symptoms related to liver disease and were detected by screening (including 12 who attended a genitourinary clinic, 12 who had screening of abnormal LFTs, six detected by the Blood Transfusion service, three detected by the Blood Transfusion Lookback exercise, nine who were screened because they had previous risk factors and five who were tested by their GP on a routine visit). Only four (7%) patients gave a history of a previous illness with jaundice. The modes of transmission of HCV were i.v. drug use in 30

Fig 1. Mode of transmission of HCV in 60 non-haemophiliac anti-HCV positive patients.

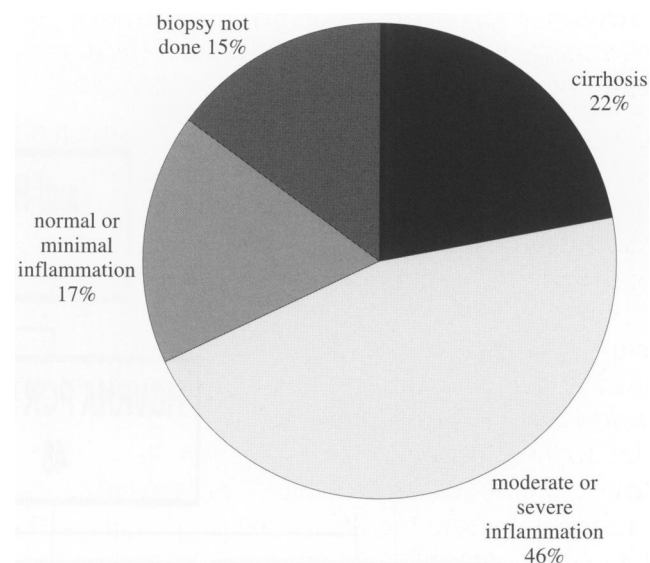


(50%), blood products in 20 (33%), sexual contacts in four (7%) and unknown in six (10%) patients (Figure 1).

Forty-eight (86%) of the 56 patients tested by PCR were positive for HCVRNA (80% of the original group, with four patients failing to attend for PCR testing). Blood investigations revealed abnormal liver biochemistry (elevated AST, ALT or GGT) in 72% of the cohort. Liver biopsy was performed in 51 (85%) patients and revealed cirrhosis in 13 (22% of the original group, Figure 2). Alcohol may have been a factor in three of the 13 cirrhotic patients. Two patients (3%) developed a hepatoma during follow-up: one patient was cirrhotic at presentation, became PCR negative with interferon therapy but relapsed on stopping treatment and died four years after presentation (aged 48 yrs); the other patient was also cirrhotic at presentation, failed to respond to interferon therapy and died one year after presentation aged 72.

Figure 3 shows the outcome of the 60 patients studied with respect to whether or not they received interferon treatment. Twelve patients were excluded as they were PCR negative. Five patients who were HCV-RNA PCR positive failed to attend for follow-up assessment and a further three patients underwent full assessment but declined the offer of treatment. Fourteen patients who were HCV-RNA PCR positive were not offered treatment due to the fact that they were either not medically fit to undergo treatment (6) or were deemed to have minimal disease activity

Fig 2. Results of liver histology for 60 non-haemophiliac anti-HCV positive patients.

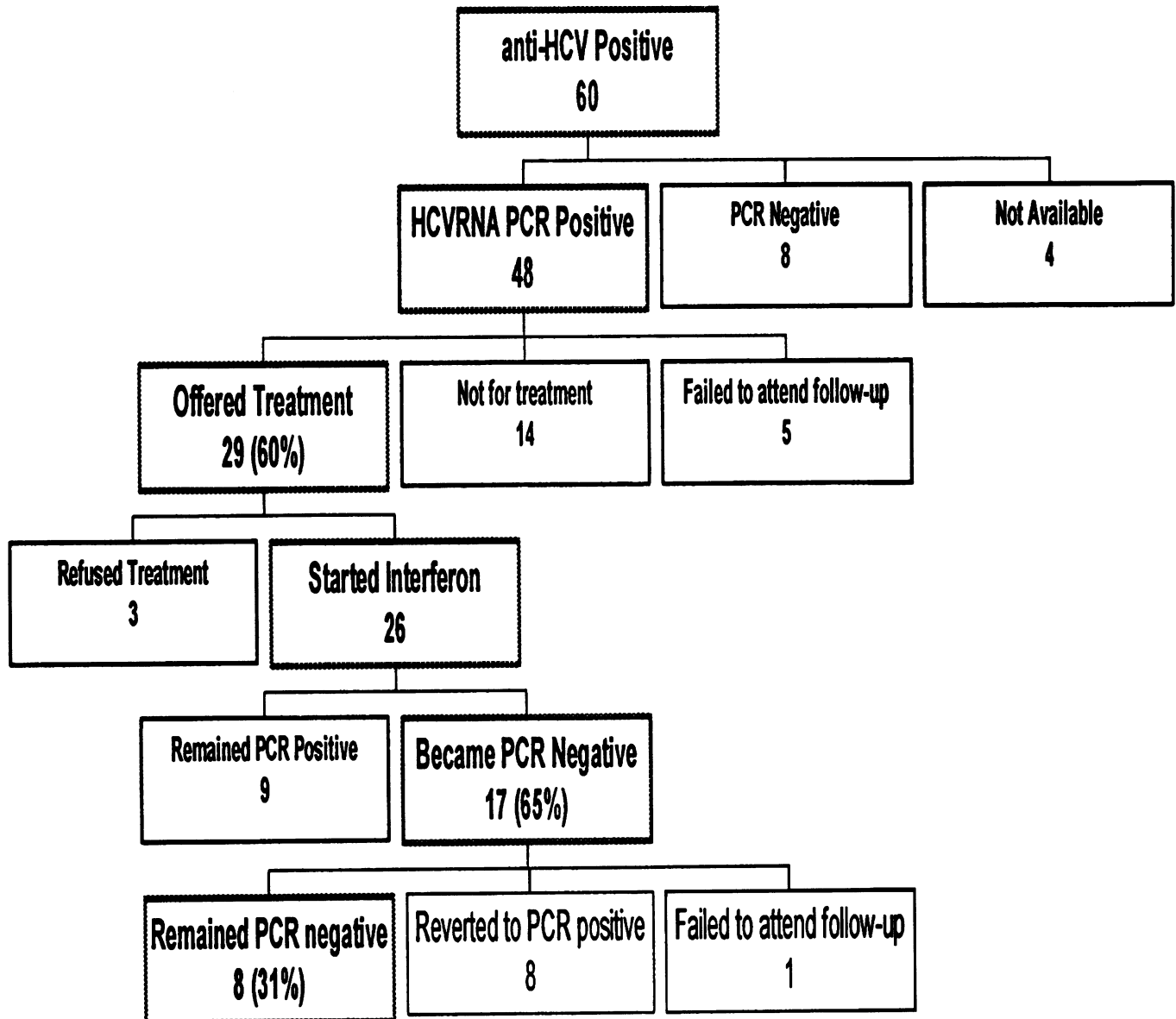


(8) based on LFTs and liver histology. This left 26 patients (43%) who were offered and accepted interferon therapy. Two patients (8%) developed thyroid dysfunction (one thyrotoxic, one hypothyroid) during interferon therapy.

Seventeen (65%) patients became HCV-RNA negative during therapy and nine remained positive (including one patient who only had 2 days of therapy, one who defaulted after just one month of interferon and four who were unable to achieve a satisfactory interferon dose or length of therapy due to side effects). Eight (31%) patients had a sustained response, remaining HCVRNA negative at least 12 months after stopping therapy, eight became HCVRNA positive again and one patient became HCVRNA negative but failed to attend for follow-up (Figure 3). Age, sex, genotype, presence of cirrhosis or mode of transmission did not significantly affect treatment success.

The Table shows the results of liver histology in 17 patients before and after interferon therapy (including three who failed to become PCR negative). The overall total scores showed no significant improvement with treatment for either grading of necroinflammatory scores ($p=0.1$) or staging of architectural change, fibrosis and cirrhosis ($p=0.55$). Assessment of the four separate components of grading showed that there was a significant improvement in the score for focal lytic necrosis, apoptosis and focal inflammation ($p=0.01$) but no significant change in the scores for piecemeal necrosis, confluent necrosis or portal inflammation.

Fig 3. Outcome of 60 anti-HCV positive non-haemophiliac patients showing HCVRNA PCR status and outcome of interferon therapy.



TABLE

Histological scores for grading and staging of chronic hepatitis in 17 patients before and after treatment of chronic HCV with interferon alpha (Modified Knodell Histology Activity Index)

	<i>Before Treatment</i>		<i>After Treatment</i>	
	<i>Grade (0 - 18)</i>	<i>Stage (0 - 6)</i>	<i>Grade (0 - 18)</i>	<i>Stage (0 - 6)</i>
P1	7	3	3	3
P2	7	3	5	3
P3	10	5	9	6
P4	8	5	4	6
P5	7	5	11	5
P6	7	5	7	5
P7	6	3	5	2
P8	6	5	6	5
P9	5	4	3	2
P10	6	1	1	1
P11	4	3	4	3
P12	4	2	2	1
P13	6	3	3	3
P14	8	5	16	6
P15	6	3	4	2
P16	8	3	4	3
P17	5	3	5	3
Overall	6(5.5-7.5)	3(3-5)	4(3-6.5)	3(2-5)
Median (IQR)			p = 0.1	p = 0.55

DISCUSSION

Estimates suggest that hepatitis C currently affects 200,000 to 400,000 people in the UK, the majority of whom have chronic HCV infection.⁸ The most important route for transmission of HCV is parenteral and the majority of those infected give a history of either intravenous drug abuse or receipt of blood/blood products prior to 1991 when screening of blood for HCV was introduced. Much less commonly, infection can be due to sexual contact, vertical transmission or non-sexual household contact. A small proportion of patients have no identifiable risk factors.

Not all patients with chronic HCV infection develop severe liver disease but 20-30% go on to develop cirrhosis after a mean of 30 years and up to 4% of cirrhotic HCV patients per year develop a hepatoma.⁶ Several factors are associated with increased risk of disease progression: age over 40

at time of infection, male sex, excess alcohol, high viral load, immune deficiency, coinfection with HIV or hepatitis B and genotype 1. Six genotypes and numerous subtypes of HCV have been identified. Genotypes 1a and 1b are by far the most common in the Western world, accounting for up to 70% of cases in the USA.⁹ This figure is thought to be closer to 50% in the UK but there are no comprehensive data.

Perhaps not surprisingly, the epidemiology of chronic HCV in Northern Ireland (based on our study sample) is in keeping with the data described above. Allowances should be made for the fact that our study group excluded haemophiliac patients who mostly acquired HCV from blood products. Genotypes 1a and 1b accounted for 57% of those whose genotype was tested and iv drug abuse was the most common risk factor accounting for half of the study group. As expected

from other data, 1 in 10 people had no identifiable risk factor for HCV. The fact that at least 22% of the study group had cirrhosis at the time of presentation is probably in keeping with the widely quoted figure of 20-30% of chronic HCV patients developing cirrhosis within 20 years.¹ This relatively high figure demonstrates the insidiously progressive nature of chronic HCV infection that can present many years after infection with advanced disease. Unfortunately we were unable to determine the length of time from initial HCV infection until presentation and therefore cannot comment on the mean time until development of cirrhosis.

The similarity between our study group demographics and other UK data¹ does not suggest that there should be any significant differences in response to treatment and the data bear this out. The initial response to interferon monotherapy treatment (61%) and subsequent sustained response rate (31%) both compare very favourably with the generally quoted initial response and sustained response rates of 47% and 20% respectively.¹ The slightly better figures we obtained should not be over-interpreted, because of the small sample size. However it could be suggested that the slightly higher response rate was due to higher doses of interferon used (5 million units thrice weekly rather than the more commonly used 3 million units thrice weekly). Liver histology data showed an improvement following therapy in some of the inflammatory parameters. Presumably if numbers had been larger it would have been possible to demonstrate a significant improvement in overall histology scores of necroinflammation and liver architecture.

The treatment data for the Northern Ireland cohort helps to illustrate one very important point regarding the number of patients treated. Given the prevalence of chronic HCV infection worldwide and the cost of treatment with interferon, the potential cost of treating the problem might seem prohibitive. Yet this study has shown that a minority of non-haemophilic patients with previous HCV infection who present to a hospital clinic actually proceed to have interferon therapy (Figure 3). A combination of factors such as minimal evidence of disease progression, unsuitability for interferon therapy and failure to comply with medical advice and follow-up resulted in only 43% of our group starting treatment. Failure to comply was one of

the most important factors accounting for almost 1 in 5 of those who had chronic HCV. Anecdotal evidence from many centres confirms that poor compliance is often a problem with non-haemophilic chronic HCV patients partly due to the large proportion who are previous or current i.v. drug abusers. One study showed that as many as 42% of patients who underwent investigation of chronic HCV infection did not want to proceed with treatment.¹⁰

In summary, based on a cohort of 60 non-haemophilic patients the epidemiology of HCV infection in Northern Ireland appears to be very comparable to elsewhere in the UK. The most common risk factor is iv drug abuse followed by contact with blood products and over half of patients are genotype 1a or 1b. Only a minority of patients actually receives treatment and response rates with interferon monotherapy compare favourably with elsewhere.

The last patient was recruited to this study in 1997 and since then there have been dramatic advances in the treatment of chronic HCV infection. Combination therapy (interferon plus oral ribavirin) has been introduced and more recently the use of pegylated interferon has improved response rates. The length of treatment is now tailored to match the specific hepatitis C genotype. In January 2004, NICE produced updated guidelines stating that combination therapy with pegylated interferon alpha and oral ribavirin is now the treatment of choice for patients with chronic HCV infection.¹¹ Studies have demonstrated that sustained response rates of 76-82% are now achievable for genotypes two and three.^{12, 13} The response rates in Northern Ireland to newer therapeutic strategies are yet to be determined.

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