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(Accepted 19 May 1997)

Management of chronic hepatitis C: clinical audit of biopsy based management algorithm

G R Foster, R D Goldin, J Main, I Murray-Lyon, S Hargreaves, H C Thomas

Abstract

Objective: To assess the attendance, outcome, compliance with treatment, and response to interferon alfa in patients with chronic hepatitis C who attended during 1995 and were treated according to a biopsy based algorithm.

Design: Retrospective audit of all patients with chronic hepatitis C attending outpatient clinics over one year.

Setting: The liver unit at a London teaching hospital.

Subjects: 255 patients with chronic hepatitis C.

Main outcome measures: Patient survival, attendance, and compliance with diagnostic and therapeutic regimens. Response to interferon alfa treatment, based on loss of viraemia three months after cessation of treatment.

Results: A large proportion of patients (39%) with newly diagnosed chronic hepatitis C infection do not want to undergo further investigation. Of those patients who do attend for further treatment, a large proportion with severe hepatic fibrosis (42%) do not want to undergo currently available treatment. The response rate to interferon (21%) in treated patients was similar to that previously reported in a trial setting. There was no significant difference in response rates in patients with or without severe fibrosis not amounting to cirrhosis. In patients with cirrhosis there was a high incidence of hepatocellular carcinoma (18%) over a follow up period of 20 months.

Conclusion: Current strategies aimed at investigating and treating patients with chronic hepatitis C are not acceptable to a large proportion of patients. Many patients with cirrhosis related to hepatitis C infection develop hepatic neoplasms, and management strategies to deal with this problem are urgently required.

Introduction

The true prevalence of chronic infection with hepatitis C virus in the United Kingdom is unknown, with current estimates suggesting that between 0.01% and 1% of the population are infected.¹⁻² The treatment requirements of these patients and the proportion who want to undergo investigation and treatment have not been studied. The optimal management of infected patients is unknown. Long term follow up studies indicate that up to 30% of infected patients will develop cirrhosis and liver tumours within 30-40 years of infection.³ Hence a large proportion of infected patients may not develop important disease and, as transmission of hepatitis C to non-sexual and sexual partners is rare,⁴ it is not clear whether these patients require intervention.

The only licensed treatment for chronic hepatitis C is a 6-12 month course of interferon alfa, which is associated with considerable side effects⁵ and costs. In clinical trials only 20% to 25% of treated patients show a sustained response.⁶⁻⁸ A balance must therefore be struck between treating all patients, resulting in side effects in patients who are unlikely to develop serious disease, or treating none, leading to an increase in mortality in those with progressive disease. Although

Liver Unit and Department of Histopathology, Department of Medicine, Imperial College School of Medicine at St Mary's, London W2 1PG

G R Foster, senior lecturer in medicine

R D Goldin, consultant histopathologist

J Main, senior lecturer in infectious diseases and medicine

H C Thomas, professor of medicine

Chelsea and Westminster Hospital, London SW10 9NH

I Murray-Lyon, consultant gastroenterologist

Kensington and Chelsea and Westminster Health Authority, London W2 6LX

S Hargreaves, director of public health

Correspondence to: Dr Foster.

BMJ 1997;315:453-8

factors that increase the likelihood of a patient developing serious disease have been identified, there is no reliable test (or combination of tests) that can predict whether an individual patient will develop a benign or a serious illness, and thus patients and their doctors are obliged to make management decisions in the absence of reliable prognostic information. Some authorities have advocated a virological approach that entails treating all patients with interferon alfa and modifying treatment to include experimental drugs when virological assays indicate a high probability of failure of treatment.⁹ Although such regimens may result in an increase in the proportion of patients who are cured, "virus based" treatment entails treating many patients with non-progressive disease. We and others have advocated a "patient based" approach.¹

We propose that patients should be treated only if they have evidence of progressive liver disease, and treatment for patients with benign disease should be postponed until more successful or acceptable treatments are developed. Such an approach may maximise the benefits of treatment. We have developed clinical guidelines for the management of patients with chronic hepatitis C, outlined in figure 1.¹ Our guidelines were first proposed in 1995 and are similar to those devised by the consensus meeting of the National Institutes of Health this year (J Hoofnagle, European Association for the Study of Liver meeting, London, 1997. All patients with antibodies against hepatitis C are tested for viraemia by the polymerase chain reaction. Patients with positive results undergo liver biopsy, which is scored according to the system devised by Ishak et al.¹⁰ Patients with moderate or severe disease (necroinflammatory score of 4 or more or a fibrosis score of 3 or more) are offered treatment with interferon for three months. After three months treatment is discontinued in those who have not responded (positive by polymerase chain reaction) as previous studies have shown that these patients are unlikely to respond to further treatment.¹¹ Interferon is continued for a further nine months in those who have lost virus after three months' treatment. Treatment is postponed in patients with mild disease. Patients with cirrhosis have a low probability of responding to interferon alfa,⁶⁻⁹ but these patients are at high risk of developing decompensated liver disease or hepatocellular carcinoma, or both, and the benefits of successful treatment may be great.¹² All patients with cirrhosis are offered interferon alfa but we explain to them that the chance of complete response is less than 10%. All our patients with cirrhosis are screened for the development of hepatocellular carcinoma with liver ultrasound and estimations of α fetoprotein every three months.

These clinical guidelines (the St Mary's Hospital algorithm) have been applied in our hospital for one year, and here we report that a high proportion of infected patients do not want to undergo treatment and that in those who do want to receive treatment the algorithm is acceptable. The response rates for treatment are also in line with those from published clinical trials. Furthermore, study of our patients with cirrhosis has revealed a higher rate of development of hepatocellular carcinoma than expected.

Fig 1 Clinical algorithm for management of patients with chronic hepatitis C infection

Subjects and methods

Letters from all hepatology clinics during 1995 were reviewed and patients with chronic hepatitis C infection identified and further details obtained from the clinical records. All patients were managed according to the algorithm outlined above.

At the first clinic attendance all patients were seen by a senior member of staff (senior registrar or consultant) and blood samples taken for liver function tests, markers of viral hepatitis (hepatitis C antibodies by second generation recombinant immunoblot assay (RIBA), hepatitis B surface antigen, hepatitis B antigen, hepatitis B antibody, hepatitis B surface antibody, and hepatitis B core antibody) as well as samples for polymerase chain reaction testing. Patients were not routinely tested for infection with HIV, but patients considered to be at risk were encouraged to undergo appropriate counselling and testing. Patients received a full explanation of the nature of their illness and the known risks of transmission. At the second attendance, when the result of the polymerase chain reaction test for hepatitis C viraemia was known, patients were provided with advice and information leaflets regarding the possible outcome of chronic hepatitis C infection and were offered counselling by an experienced nursing sister. The possible benefits of treatment were explained, and patients were offered a liver biopsy to determine the severity of their disease and to exclude other causes of hepatic injury.

Patients who agreed to undergo a liver biopsy were seen after the procedure and offered treatment with interferon alfa if the biopsy showed evidence of moderate or severe disease; during the first six months this was defined as marked inflammation or severe

Fig 2 Patient attendance and compliance in existing patients with chronic hepatitis C infection seen at St Mary's Hospital in 1995. Figures in parentheses are proportions of patients undergoing liver biopsy with designated histological finding

fibrosis. During the latter half of 1995 a biopsy scoring system was introduced based on the modified HAI system¹⁰ and moderate or severe disease was redefined as a fibrosis score of 3 or more or a necroinflammatory score of 4 or more. Review of the biopsies taken during the first half of the year showed that the decision to offer treatment was the same regardless of the histological system used. Patients were treated with recombinant interferon alfa at a dose of 4.5 mU three times a week given by self administered subcutaneous injection under supervision. Treatment was modified after three months in accordance with our clinical algorithm.

Results

A total of 255 new and existing patients with chronic hepatitis C were reviewed during 1995. Two patients had other viral infections (chronic hepatitis B) and were excluded from further analysis. The mean age of patients infected with hepatitis C was 42.8 years, and 90 were female.

Attendance and compliance

Existing patients—We reviewed 140 patients with known chronic hepatitis C infection during 1995. Figure 2 shows their outcome and attendance. Twenty one were lost to subsequent follow up. Five previously treated patients were negative by polymerase chain reaction, and one patient lost hepatitis C RNA during the year. Hence 114 infected patients were reviewed and underwent liver biopsy (either during the year or during a previous assessment). Five biopsies were inadequate for formal assessment, and these patients were classified according to the information available

Table 1 Source of referral, risk factors, and subsequent attendance for patients referred during 1995 with chronic hepatitis C infection who were medically fit and initially agreed to further investigation

Detail	Attended (n=55)	Did not attend (n=35)
Source of referral:		
General practitioner	33	4
Genitourinary clinic	13	29
Hospital consultant	6	1
Other*	3	1
Risk factor†:		
Injecting drug user	23	19
Unknown	21	14
Transfusion	11	2

*Mainly from accident and emergency departments.

†Patients newly diagnosed.

from the biopsy report (two had mild disease and three had moderate or severe disease). Thirty five patients (32%) had cirrhosis, 40 (35 %) had moderate or severe disease, and 38 (33%) had mild hepatitis.

New patients—One hundred and thirteen patients with antibodies against hepatitis C were referred in 1995. Figure 3 shows the outcome for these patients. Fifteen patients had normal results of liver function tests at presentation and repeat polymerase chain reaction testing for hepatitis C RNA yielded negative results in nine of these cases, thus the polymerase chain reaction assay identified six infected patients with normal liver function. Twenty four patients (23% of those who were positive by polymerase chain reaction) attended further but declined investigation—eight had pre-existing medical conditions that precluded investigation of their liver disease, and 16 patients decided to

Fig 3 Patient attendance and compliance in new patients with chronic hepatitis C infection seen at St Mary's Hospital in 1995. Figures in parentheses are proportions of patients undergoing liver biopsy with designated histological finding

Fig 4 Outcomes in 39 patients with cirrhosis associated with hepatitis C infection followed up for a maximum of 22 months

postpone investigation. A large proportion (35; 33%) of new referrals did not attend for further follow up (table 1), and this was most marked for patients referred by the department of genitourinary medicine; 29 (69%) of these patients did not attend for follow up. Most patients admitted to previous or current injecting drug use but a large proportion of patients (34; 33%) had no obvious risk factor for hepatitis C infection. Table 1 shows the risk factors for infection and subsequent attendance for newly diagnosed patients. Forty six new patients underwent a liver biopsy; in seven cases (one with moderate or severe disease and six with mild disease) the sample was either too small for formal scoring or the biopsy was performed at another institution and the results were not available to us. These biopsies were evaluated according to the information available from the histology report (as above). Histological evaluation of the 46 new patients showed that 5 (10%) had cirrhosis, 20 (44 %) moderate or severe hepatitis, and 21 (46 %) mild hepatitis.

Outcomes in patients with cirrhosis

Forty patients with compensated cirrhosis were seen during 1995; one was referred with known hepatocellular carcinoma and was excluded from our analysis of patient outcome. The mean age of the patients with cirrhosis (53 years) was significantly higher than that for patients with mild disease (40 years) or moderate or severe disease (44.5 years) ($P < 0.001$). The 39 patients with cirrhosis and no evidence of hepatocellular carcinoma at their first attendance in 1995 have now been followed for a maximum of 22 months; figure 4 summarises their outcome. Seven patients (18%) developed hepatocellular carcinoma and in four transplantation was performed: one patient died of pneumocystis pneumonia after surgery, and the others are alive and well. One patient with hepatocellular carcinoma judged too large for surgery died, and the two other patients with tumours that were not suitable for transplantation underwent chemoembolisation (one patient) and intralesional alcohol treatment (one patient). Both are alive but showing signs of disseminated malignancy. Three patients developed decompensated liver disease: in one transplantation was performed but the patient died after an episode of sepsis, and the other two patients recently died.

All patients with cirrhosis were considered for interferon alfa treatment: three patients had other medical conditions precluding such treatment, and 21 patients accepted an offer of treatment (table 2). Two patients discontinued treatment because of side effects, and after three months' treatment two patients were aviraemic (negative by polymerase chain reaction). Only one of these patients remained negative three months after interferon alfa treatment. Ten patients who failed to respond to three months' interferon alfa accepted treatment for six months with a combination of interferon alfa plus ribavirin (800 mg per day). One patient became anaemic, and treatment was withdrawn, and one patient developed hepatocellular carcinoma while on treatment. Of the eight patients who completed six months of treatment, two (25%) remained negative by polymerase chain reaction three months after cessation of treatment. Hence combination treatment with interferon alfa plus ribavirin may lead to a virological cure in a small proportion of patients with cirrhosis who fail to respond to interferon alfa alone.

In view of recent reports suggesting that interferon alfa, even if unsuccessful in eradicating viraemia, may prevent the subsequent development of hepatocellular carcinomas¹² we examined the effects of treatment in our cohort of patients. Sixteen patients did not receive interferon alfa, and four developed hepatocellular carcinoma. Ten patients received interferon alfa alone, and one developed a tumour. Of the 10 patients treated with interferon alfa plus ribavirin, three (30 %) developed hepatocellular carcinoma. There was no significant difference in the proportion of patients developing tumours in these three treatment groups, although the number of patients was far too small to detect anything other than gross differences.

Sixty patients had moderate or severe hepatitis, and 33 accepted treatment with interferon alfa: 10 were new referrals and 23 were existing patients (table 2). Four patients could not tolerate treatment, and in seven (20%) a sustained response to interferon alfa (negative by polymerase chain reaction with normal results on liver function tests at least three months after cessation of treatment) was achieved. Four patients with moderate or severe hepatitis who did not respond to interferon alfa after three months' treatment were treated with interferon alfa plus ribavirin for a further six months, and in two patients polymerase chain reaction testing after six months of combination treatment was negative. One of these patients has been followed for a further three months and remains aviraemic, the other patient has been lost to follow up.

Patients without cirrhosis

Fifty nine patients had mild disease that, in our view, did not require immediate treatment. Their mean age (40 years) was significantly lower than the mean

Table 2 Response to interferon alfa in patients with differing degrees of liver damage

Detail	Mild hepatitis	Moderate or severe hepatitis	Cirrhosis
No who started treatment	13	33	21
No (%) who:			
Stopped treatment because of side effects	2 (15)	5 (15)	2 (10)
Were non-viraemic after 3 months of treatment	4 (30)	15 (55)	2 (10)
Were non-viraemic 3 months after stopping treatment	2 (30)	7* (21)	1 (5)

*One patient who started treatment in late 1995 has not yet completed it and follow up.

age of patients with moderate or severe disease (44.5 years; $P < 0.05$, t test). Thirteen patients wanted to receive interferon alfa and were treated. Two could not tolerate it, and three patients achieved sustained viral clearance (table 2). Two patients who failed to respond to three months of interferon alfa were treated with it plus ribavirin for a further six months, but none achieved a sustained cessation of viral replication. There was no significant difference in the short term response to interferon alfa in patients with moderate or severe or mild disease ($P > 0.05$, χ^2 test).

Eight patients who received treatment with interferon alfa for one year relapsed when treatment was discontinued. Serial samples (at least once a week for four weeks) after treatment were obtained from five patients and revealed that in two cessation of treatment was followed by a severe hepatitis (serum alanine transaminase > 10 times the upper limit of normal) within four weeks of stopping interferon alfa. None of these patients developed hepatic encephalopathy, and in all the serum samples alanine transaminase returned to within 10 times the upper limit of normal within a few months. The significance of this rebound hepatitis is unknown.

Discussion

The large number of patients chronically infected with hepatitis C poses a considerable challenge to health-care providers. To determine the treatment requirements of these patients and to optimise the benefits of treatment we have introduced treatment guidelines¹ and have completed a review of the effectiveness of these guidelines.

Non-attendance of patients with hepatitis C

The most striking feature of this audit is the high rate of non-attendance in patients with newly diagnosed hepatitis C infection. This was most obvious in patients who had a history of injecting drug use or were referred from the genitourinary clinic, or both. The genitourinary clinic at St Mary's is used by many patients with high risk behaviour (injecting drug use or high risk sexual activity) as a walk in assessment centre where they can undergo confidential screening for various infections. It is therefore not surprising to find that many of these patients do not reattend St Mary's for further follow up. Until the reasons for the high drop out rate in these patients are identified and rectified, however, it is apparent that intervention based approaches for hepatitis C cannot be targeted at patients from this clinical area.

Treatment of patients with chronic hepatitis C

Modern medical management is a collaborative effort between the physician and patient. Patient involvement in the decision making process is particularly important in conditions for which the optimal treatment is still undetermined and treatment is associated with significant side effects. Our policy is to counsel all patients with viral hepatitis and to provide them with sufficient information to reach an informed decision regarding future management. The data presented here indicate that, at present, many patients do not wish to undergo treatment for chronic hepatitis C infection. The reasons for this may include concern

regarding the poor efficacy and relatively high side effects of interferon alfa, belief (appropriate or otherwise) that their liver disease will not progress, and confidence that the pharmaceutical companies will shortly develop more effective or less toxic treatments.

The best management of chronic hepatitis C in patients who do want to be treated is still debated. There is no firm evidence to show that patients with fibrosis on a liver biopsy are more likely to develop cirrhosis than patients whose biopsy does not show fibrosis. In other progressive liver diseases, however, fibrosis is associated with a poor prognosis, and one recent report suggests that this is indeed the case for patients with chronic hepatitis C.¹³ In the absence of evidence to the contrary, we have assumed that patients with fibrosis or severe necroinflammation, or both, are more likely to develop complications related to hepatitis C infection in the near future and are therefore candidates for priority treatment. Restricting treatment to these patients reduces the overall prevalence of side effects, but we recognise that it may result in a failure to treat patients who are at risk of serious liver disease. Clearly it is too early to assess the effects of our policy on complications related to hepatitis C in patients without cirrhosis but all patients with chronic hepatitis C are regularly reviewed and, to date, no serious complications have developed in patients without cirrhosis who have not been treated. It will be important to document whether patients with moderate or severe disease who have declined treatment will develop more complications than patients with mild disease in whom we have withheld treatment. Some studies on interferon alfa have suggested that patients with fibrosis not amounting to cirrhosis have poorer response rates to treatment,¹⁴ although this has not been confirmed in other studies.¹⁵ Our data show that for patients in the United Kingdom response rates are similar in patients with and without severe fibrosis (short of cirrhosis), suggesting that delaying treatment in patients with mild disease will not reduce their subsequent chances of a successful response to interferon alfa. In patients who have developed cirrhosis, however, our data confirm previous observations that indicate at least a halving of response rates to interferon alfa.^{14 15} It is therefore important to treat patients before cirrhosis has developed.

A considerable proportion of patients with chronic hepatitis C who are treated with interferon alfa develop intolerable side effects, chiefly depression, and discontinue treatment. Default rates in our patients were considerably higher than those in previous studies and may be related to the long periods of treatment that are required; patients may be willing to tolerate mild depression for a short period but are not prepared to accept this long term.

Cirrhosis related to hepatitis C

The outcome for patients with advanced cirrhosis related to hepatitis C infection is unknown. Several studies indicate that such patients are at risk of developing hepatocellular carcinoma, and studies from Japan indicate that up to 10% of patients will develop it over a two year period.¹² In our series a significant proportion (18%) have developed hepatocellular carcinoma during our two years of follow up. This high rate may be due to

Key messages

- The optimal management for patients with chronic hepatitis C is controversial
- This study reviews the outcome of patients managed accordingly to algorithm based on liver biopsy results
- Many patients with chronic hepatitis C infection either do not want to undergo further investigation or decline treatment with interferon
- Management according to an algorithm based on biopsy results is acceptable to patients and leads to response rates (21%) in line with those of clinical trials
- A large proportion of patients with cirrhosis related to hepatitis C (18%) developed an hepatocellular carcinoma during follow up of 20 months

referral bias—patients with more aggressive disease may be more likely to be referred to an academic unit—but the high incidence of development of hepatocellular carcinoma in patients with cirrhosis associated with hepatitis C infection is clearly a matter of concern and indicates that strategies to prevent the development of cirrhosis should be pursued as should treatments that may reduce the rate of hepatocellular carcinoma in patients with cirrhosis. The number of patients studied is too small to assess risk factors for the development of hepatocellular carcinoma and the effect of earlier treatment with interferon alfa with and without ribavirin. The optimal management of patients with cirrhosis associated with hepatitis C infection is not yet known. We have adopted a policy of vigorous screening (three monthly ultrasonography) to detect early neoplasms so that transplantation can be considered, and our data suggest that this policy is advantageous: four patients with potentially curable tumours were detected and have now undergone transplantation surgery. The remainder received intralesional alcohol or chemoembolisation.

As many patients with cirrhosis associated with hepatitis C infection will develop serious complications within a short time frame and respond poorly to current licensed treatments, it is important to treat these patients before cirrhosis has developed. It is clear from our audit, however, that many patients with hepatitis C are not prepared to accept currently available treatment: many default from further follow up, others decline treatment. Currently clinical studies of combination treatment with interferon alfa and the oral nucleoside derivative, ribavirin, are showing promise in small scale clinical studies,¹⁶ and our data confirm that a small proportion of patients who do not respond to interferon alfa on its own may benefit from combination treatment. Large clinical trials are currently being established to assess the efficacy of this dual treatment, and it remains to be seen whether therapeutic combinations that include interferon alfa will be more acceptable to patients because of improved response rates. Novel therapeutic agents that are more acceptable to patients will probably be required to deal with the large number

of patients infected with hepatitis C. If the high incidence of hepatocellular carcinoma in patients with cirrhosis is confirmed in other studies, these patients should be warned of this complication and encouraged to undergo regular screening by ultrasonography and estimation of a fetoprotein.

We thank Drs G Alexander and A Gimson and the transplantation team at Addenbrookes Hospital, Cambridge, for their help with our patients requiring transplantation.

Funding: None.

Conflict of interest: GRF, RDG, JM, IM-L and HCT have participated in drug company sponsored trials of interferon in the management of patients with chronic hepatitis C.

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(Accepted 19 May 1997)

Correction

Intersalt revisited: further analyses of 24 sodium excretion and blood pressure within and across populations

An author error, only recently noticed, occurred in this paper last year by Professor Elliott and others (18 May 1996, pp 1249-53). The values in the second line of data in table 3 should have read 8.8, 5.2, 5.3, and 5.7 [not 10.1, 5.5, 6.2, and 6.3]. The probabilities remain the same. A related error occurred in a commentary by the same group of authors to another article in the same issue (pp 1285-7). The numbers in the second of the four sets of plots in figure 1 should have read b (SE) = 9.0 (1.7) mm Hg [for 52 samples] and b (SE) 7.0 (2.9) mm Hg [for 48 samples].