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Dipartimento di Medicina Interna, Cardioangiologia ed Epatologia, Università di Bologna, Bologna, Italy
A Gramenzi
P Andreone
S Fiorino
D Magalotti
C Cursaro
V Arienti†
M Zoli
G Gasbarrini‡
M Bernardi

Istituto Metodologie Diagnostiche Avanzate, Consiglio Nazionale delle Ricerche, Palermo, Italy
C Cammà

Cattedra di Gastroenterologia, Clinica Medica, Università di Palermo, Palermo, Italy
M Giunta
A Craxì

Dipartimento di Medicina Interna e Gastroenterologia, Università di Bologna, Bologna, Italy
C Calabrese
G Di Febo

Dipartimento Clinico di Scienze Radiologiche ed Istopatologiche, Università di Bologna, Bologna, Italy
C Rossi

Present addresses:
†Divisione di Medicina Interna, Ospedale Maggiore, Bologna, Italy.
‡Clinica Medica, Università Cattolica del Sacro Cuore, Roma, Italy

Correspondence to:
Dr P Andreone, Semeiotica Medica, Policlinico S Orsola, Via Massarenti, 9-40138 Bologna, Italy.
andreone@med.unibo.it

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Abstract

***Background*—The role of interferon treatment on the natural history of hepatitis C virus related cirrhosis is under debate.**

***Aim*—To evaluate the effect of interferon on the clinical course of compensated hepatitis C virus related cirrhosis.**

***Patients and methods*—Seventy two cirrhotic patients treated with interferon and 72 untreated controls matched treated patients with for quinquennia of age, sex, and Child-Pugh's score were enrolled in a prospective non-randomised controlled trial. Treated patients received leucocytic interferon alfa, with an escalating schedule for 12 months. The incidence and risk (Cox regression analysis) of clinical complications (hepatocellular carcinoma, ascites, jaundice, variceal bleeding, and encephalopathy) and death were calculated.**

***Results*—Over median follow up periods of 55 months for treated and 58 for untreated subjects, seven and nine patients, respectively, died, and 20 and 32, respectively, developed at least one clinical complication (ns). Hepatocellular carcinoma developed in six treated and 19 untreated patients (p=0.018). Seven treated patients showed sustained aminotranferase normalisation and none died or developed complications. Clinical complications were significantly associated with low albumin, bilirubin, and prothrombin activity while hepatocellular carcinoma was significantly related to no treatment with interferon, oesophageal varices, and high α fetoprotein levels. By stratified analysis, the beneficial effect of interferon was statistically evident only in patients with baseline α fetoprotein levels ≥20 ng/ml.**

***Conclusions*—Interferon does not seem to affect overall or event free survival of patients with hepatitis C virus related cirrhosis while it seems to prevent the development of hepatocellular carcinoma. Patients who achieved sustained aminotransferase normalisation survived and did not develop any complications during follow up.**

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Keywords: hepatocellular carcinoma; cirrhosis; hepatitis C virus; interferon alfa

Hepatitis C virus (HCV) infection is the main cause of chronic liver disease in Italy, accounting for approximately 60% of cases.[1 2] At least 25% of patients with chronic hepatitis C will develop complications of end stage liver disease, including liver failure, portal hypertension, and hepatocellular carcinoma.[3] Indeed, chronic hepatitis C represents one of the leading indications for liver transplantation.[3] Whether or not interferon (IFN) treatment can modify the natural history of HCV related liver cirrhosis is still subject to debate. In the past few years several studies[4–15] have reported conflicting results on the effectiveness of IFN in preventing or delaying the development of hepatocellular carcinoma. The results of studies that evaluated the effect of IFN therapy in preventing other complications of cirrhosis and ameliorating the survival rate of patients are also controversial.[8 10 11 13 14 16 17] All of these studies except one[4] were retrospective and, consequently, selection bias could limit the reliability of the results. In this setting, a prospective randomised clinical trial would represent the optimal study design. However, the ethical issues related to the potential, even if not proved, protective effect of IFN and the long duration of the observation period necessary make it difficult to accomplish.[18]

Hence we performed a prospective non-randomised controlled trial aimed at assessing the impact of IFN treatment on the natural history of HCV related liver cirrhosis in terms of overall survival, survival free from disease related events, and hepatocellular carcinoma development.

Patients and methods

PATIENTS

We conducted a non-randomised prospective controlled trial at the Department of Internal Medicine, Cardioangiology and Hepatology, University of Bologna, that serves as a tertiary referral centre. Seventy two patients (mean age 58 (7) years; male/female distribution 39/33) with a diagnosis of HCV positive liver cirrhosis treated with IFN alfa in our outpatient clinic were recruited from May 1992 to May 1994. Patients never treated with IFN alfa, admitted to the same outpatient clinic and enrolled in a survey programme to evaluate the natural history of cirrhosis,[19] were matched with treated patients for quinquennia of age, sex, and Child-Pugh's score, and served as a control group.

Abbreviations used in this paper: HCV, hepatitis C virus; IFN, interferon; ALT, alanine aminotransferase; MU, mega units; SRs, sustained biochemical responders; TRs, transient biochemical responders; NRs, non-responders.

Treated and untreated patients were recruited on the basis of the following inclusion criteria: (1) diagnosis of liver cirrhosis; (2) abnormal serum alanine aminotransferase (ALT) levels for at least one year before entry; (3) seropositivity for anti-HCV; (4) absence of hepatitis B surface antigen and all other potential causes of chronic liver disease; (5) human immunodeficiency virus seronegativity; (6) no history or clinical evidence at enrolment of complications of cirrhosis (that is, ascites, gastrointestinal bleeding, hepatic encephalopathy, or jaundice); and (7) no evidence of hepatocellular carcinoma at entry into the study on the basis of ultrasound examination and normal α fetoprotein levels. In cases with elevated α fetoprotein levels (≥20 ng/ml) computed tomography of the liver was also performed.

Patients with alcohol abuse, defined as alcohol intake ≥60 g/day, were excluded. No patient was treated with diuretics.

Diagnosis of liver cirrhosis was biopsy proven in 57 (79%) IFN treated patients and in 48 (67%) controls. In the other cases the diagnosis was unequivocal by the presence of the following criteria: (1) oesophageal varices at endoscopy or (2) thrombocytopenia (≤100 000/mm^3) with ultrasound signs of portal hypertension.

All patients underwent endoscopic evaluation of the upper gastrointestinal tract, and oesophageal varices were classified according to Beppu and colleagues.[20]

FOLLOW UP

Entry into the study of treated patients was defined as the start of treatment. The interval between diagnosis of HCV compensated cirrhosis and the start of therapy was less than six months. Entry into the study of untreated patients was defined as the time we made the diagnosis of HCV cirrhosis or when patients with known cirrhosis were first referred to us.

Total duration of follow up was calculated from the date of entry until death, liver transplantation, or the end of the observation period (30 April 1998). Patients who were lost to follow up were censored in the statistics at the time of dropout.

Treated patients received leucocytic IFN alfa (Alfaferone; Alfa Wassermann, Italy) with an escalating schedule based on biochemical response. Treatment started with 1 mega unit (MU) three times weekly for three months and the dose was progressively increased every three months to 3, 6, and 9 MU if a complete biochemical response was not achieved. In the case of a breakthrough (defined as increasing serum ALT levels above the upper normal limit during IFN treatment occurring after an initial biochemical response), the IFN dose was increased at the time of the event. Duration of treatment was 12 months and median total dose of IFN was 741 MU (range 160–1087). The total dose of IFN was defined as low if it was ≤468 MU, medium if 469–780 MU, and high if >780 MU.

Patients treated with IFN were divided into the following three groups on the basis of the change in serum ALT levels: (1) sustained biochemical responders (SRs) if ALT levels remained within the normal range for more than six months after the end of therapy; (2) transient biochemical responders (TRs) if ALT levels decreased to the normal range during therapy but then increased to abnormal levels within six months from the end of therapy; and (3) non-responders (NRs) if ALT levels did not normalise during therapy.

Treated patients underwent clinical and laboratory assessment monthly during IFN treatment and quarterly thereafter, as did their untreated counterparts. In both groups we examined α fetoprotein levels every three months and performed a liver ultrasound examination every six months. Death was classified as liver related (liver failure, gastrointestinal bleeding, renal failure, infections) or not liver related. To calculate survival times, liver transplantation was combined with death.

The following complications were defined as events: development of ascites (clinical and/or ultrasound finding), jaundice (serum bilirubin >3 mg/dl), clinical hepatic encephalopathy, gastrointestinal bleeding (haematemesis and/or melena), and occurrence of hepatocellular carcinoma. If hepatocellular carcinoma was suspected on the basis of increasing levels of α fetoprotein and/or ultrasound findings, diagnosis was established or excluded on the basis of hepatic arteriography with Lipiodol followed by computed tomography.

STATISTICAL ANALYSIS

Continuous variables were expressed as mean (SD). The χ^2 and Student's t tests were performed as appropriate; all p values were two tailed. The Kaplan-Meier method was used to estimate the length of survival and survival without clinical events.[21] Differences in these incidences were assessed by the log rank test. The following variables were considered for univariate analysis: age, sex, baseline ALT, platelets, albumin, prothrombin activity, bilirubin, alkaline phosphatase, γ-glutamyltransferase, α fetoprotein, oesophageal varices, and IFN treatment.

The Cox proportional hazard model[22] was used to assess survival, and event free and cancer free survival in a multiple regression analysis. All analyses were conducted with SAS version 6.08.[23] For Cox regression, the PHREG procedure was used. All p values were two tailed and all confidence intervals (CIs) were 95%. We verified that the most important issue of the Cox's model—that is, the assumption of proportional hazard—was not violated. The proportional assumption was also checked using analytical and graphical methods. The log minus log plot (that is, the logarithm of the cumulative hazard function) was used to examine the proportionality assumption of the model. The vertical equidistance between the curves for all variables shows that the assumption does not seem to be violated. Moreover, we performed a test of trend in the hazard ratio by adding a new variable to the model, representing the interaction effect between the prognostic variable and follow up time. As this

Table 1 Baseline features of patients according to interferon (IFN) treatment

	Treated (n=72)	*Untreated (n=72)*	*p Value*
Mean age (y)	57.9 (7.2)	58.1 (7.8)	NS
Sex (M/F)	33/39	33/39	NS
Child-Pugh class (A/B)	60/12	60/12	NS
ALT (IU/l)	147 (74.8)	89 (64)	0.0001
Platelets (×1000/mm^3)	108.8 (38.4)	140.3 (74)	0.003
Albumin (g/dl)	3.8 (0.4)	3.8 (0.5)	NS
Prothrombin activity (%)	76.7 (12.8)	77.2 (13.8)	NS
Bilirubin (mg/dl)	1.0 (0.6)	1.1 (0.5)	NS
Alkaline phosphatase (IU/l)	264.5 (90.9)	240.8 (97)	NS
γ-Glutamyltransferase (IU/l)	65 (47.1)	76.4 (56.2)	NS
α-Fetoprotein (n (%))			
<20 ng/ml	50 (69)	60 (83)	0.05
⩾20 ng/ml	22 (31)	12 (17)	
Oesophageal varices (n (%))			
0	44 (61)	23 (32)	
F1	18 (25)	42 (58)	0.04
F2/F3	10 (14)	7 (10)	
IFN doses (n (%))			
Low (⩽468 MU)	18 (25)	—	
Medium (469–780 MU)	30 (42)	—	—
High (>780 MU)	24 (33)	—	

Values are mean (SD) or number (%).
Normal values: alanine aminotransferase (ALT) <40 IU/l, alkaline phosphatase <280 IU/l, γ-glutamyltransferase <50 IU/l.

variable was not statistically significant we can conclude that there was no trend (increase or decrease) over time in the hazard ratio.

Results

Baseline characteristics of treated and untreated patients are reported in table 1. The two groups were similar, although α fetoprotein levels ⩾20 ng/ml were more frequently observed among treated patients and oesophageal varices among untreated patients.

In the treated group, seven patients (10%) were classified as SRs, 16 (22%) as TRs, and the remaining 49 (68%) as NRs. Four SRs received a low and three a medium dose of IFN; among TRs, seven subjects received a low dose, five a medium, and four a high dose of IFN; seven NRs received a low dose, 22 a medium, and 20 a high dose of IFN. After five years of follow up, four treated (5.5%) and three untreated (4.1%) patients were lost to follow up. Median follow up was 55 months (range 2–70) in the treated group and 58 months (range 27–71) in the untreated group.

SURVIVAL

Seven treated (10%; two TRs, five NRs) and nine untreated (12.5%) patients died during the observation period. Two treated (both NRs) and two untreated patients were transplanted because of liver failure. In treated patients, the causes of death were liver failure in five, variceal bleeding in one, and hepatocellular carcinoma in one. Among untreated patients, five died because of liver failure, two from variceal bleeding, one from hepatocellular carcinoma, and one from a non-liver related event. Median survival was 48 months (range 13–60) for treated and 52 months (range 37–60) for untreated patients. Length of survival was not significantly different between treated and untreated patients (fig 1A).

CLINICAL COMPLICATIONS

Twenty treated (28%; eight TRs, 12 NRs) and 32 untreated (44%) patients developed at least one clinical complication. No significant difference was found in event free survival between

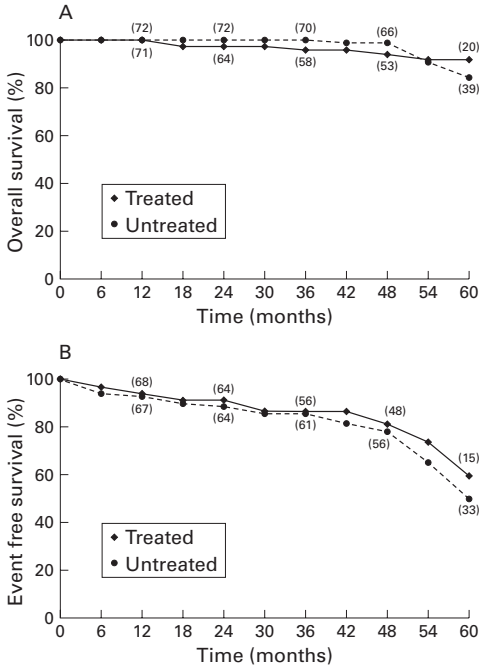

Figure 1 (A) Cumulative probability of overall survival and (B) event free survival in treated and untreated patients. Number of patients at risk are shown in parentheses.

treated and untreated patients (fig 1B). Among the clinical complications, hepatocellular carcinoma was the most frequent (six treated patients and 19 untreated), followed by ascites (11 treated and 11 untreated patients), gastrointestinal bleeding (two treated and one untreated), and clinical hepatic encephalopathy (one treated and one untreated).

In the univariate analysis (table 2), six baseline variables were significantly associated with the risk of clinical complications: decreased platelet count, low albumin, low total bilirubin, high alkaline phosphatase, low prothrombin activity, and oesophageal varices. In multivariate analysis (table 3), only albumin, total bilirubin, and prothrombin activity proved to be independent risk factors for the occurrence of clinical complications.

Hepatocellular carcinoma

With regard to the occurrence of hepatocellular carcinoma, six treated patients who failed to develop SR (8%; two TRs and four NRs) and 19 untreated (26%) developed hepatocellular carcinoma during the observation period. Among the six treated patients who developed hepatocellular carcinoma, four received a low and two a medium dose of IFN.

The cumulative probability of developing hepatocellular carcinoma in treated patients was 1.5% and 11% at two and five years, respectively, and 11% and 27%, respectively, in untreated patients (fig 2A). These differences were statistically significant (p=0.0006 and p=0.013, respectively). In the univariate analysis (table 4), five baseline parameters were significantly associated with the risk of hepatocellular carcinoma: low albumin, low prothrombin activity, oesophageal varices, increased α fetoprotein levels, and absence of

Table 2 Univariate analysis of risk factors for event free survival

	Event (n=52)	*No event (n=92)*	*p Value*
Mean age (y)	58.9 (8.2)	57.6 (7.1)	NS
Sex (M/F)	24/28	42/50	NS
ALT (IU/l)	103.2 (63.4)	126.9 (80.5)	NS
Platelets (×1000/mm³)	105.9 (55.3)	135.1 (62)	0.002
Albumin (g/dl)	3.6 (0.5)	3.9 (0.4)	0.0001
Prothrombin activity (%)	71.7 (14.8)	80 (11.4)	0.0001
Bilirubin (mg/dl)	1.4 (0.7)	1.0 (0.5)	0.0001
Alkaline phosphatase (IU/l)	278.3 (94.6)	238.2 (92.3)	0.01
γ-Glutamyltransferase (IU/l)	66.9 (42.8)	72.9 (56.6)	NS
α-Fetoprotein (n (%))			
<20 ng/ml	36 (69)	74 (80)	NS
⩾20 ng/ml	16 (31)	18 (20)	
Oesophageal varices (n (%))			
0	15 (29)	52 (56)	
F1	28 (54)	32 (35)	0.006
F2/F3	9 (17)	8 (9)	
IFN treatment (n (%))			
Yes	20 (38.5)	52 (56.5)	NS
No	32 (61.5)	40 (43.5)	

Values are mean (SD) or number (%).
Normal values: alanine aminotransferase (ALT) <40 IU/l, alkaline phosphatase <280 IU/l, γ-glutamyltransferase <50 IU/l.

Table 3 Adjusted relative risk of event free survival in 72 patients treated with interferon and 72 untreated controls

Variable	*Code*	*β*	*SE*	*p Value*	*Odds ratio*	*95% CI*
Albumin level	0: ⩽3.5 g/dl					
	1: >3.5 g/dl	−1.34	0.30	<0.0001	0.26	0.15–0.47
Bilirubin level	0: ⩽1.0 mg/dl					
	1: >1.0 mg/dl	0.61	0.30	0.04	1.8	1.03–3.33
Prothrombin activity	Continuous					
		−0.03	0.01	0.015	0.97	0.95–0.99

Model χ^2=49.06 with 6 df, p<0.0001. Adjusted for baseline platelet count, alkaline phosphatase levels, and variceal size.
SE, standard error.

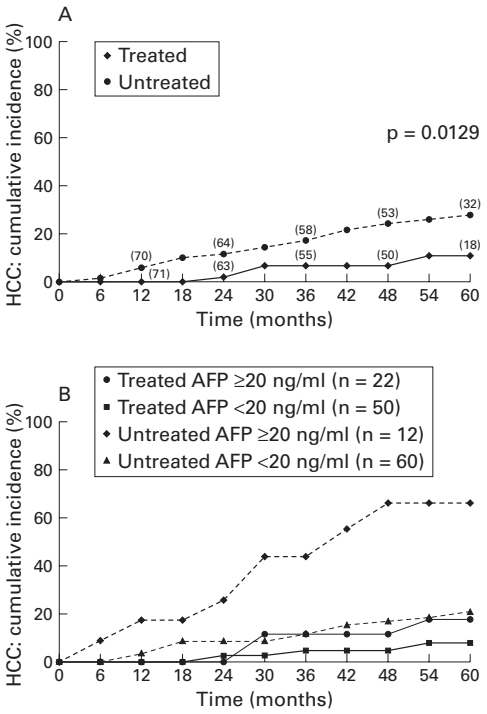

Figure 2 (A) Cumulative probability of hepatocellular carcinoma (HCC) among treated and untreated patients. (B) Cumulative probability of HCC among treated and untreated patients according to baseline α fetoprotein (AFP) serum levels (treated AFP <20 ng/ml v untreated <20 ng/ml, ns; treated AFP ⩾20 ng/ml v untreated AFP ⩾20 ng/ml, p=0.0026). Number of patients at risk are shown in parentheses.

IFN treatment. In multivariate analysis (table 5), only α fetoprotein, size of varices, and IFN treatment were independent risk factors for hepatocellular carcinoma. Untreated patients had a risk of developing hepatocellular carcinoma 4.3-fold higher (CI 1.6–11.4) than those treated with IFN. This risk has the same magnitude as that exhibited by patients with baseline α fetoprotein levels ⩾20 ng/ml. When treated and untreated patients were stratified according to baseline α fetoprotein levels (⩾20 or <20 ng/ml), untreated patients had a cumulative incidence of hepatocellular carcinoma significantly higher than those treated only in the strata with α fetoprotein ⩾20 ng/ml (p=0.003) (fig 2B).

Discussion

The role of IFN in preventing complications of HCV related cirrhosis is controversial. To date, only one randomised study reported a significant reduction in the incidence of hepatocellular carcinoma in patients treated with IFN compared with untreated subjects.[4] However, this study has been subjected to many criticisms[5 18 24 25] because of methodological flaws. After this first report, many retrospective studies aimed at assessing the impact of IFN on the long term outcome of HCV related cirrhosis were published[6–16] but their results are largely inconsistent. This can be explained, at least in part, by differences in design, stage of disease, duration of follow up, type of IFN, and schedule of treatment. The main reason for such discrepancies however most likely derives from the many limitations of retrospective studies, such as susceptibility, intervention, and selection biases, that may make the results unreliable.[26] A randomised clinical trial would be the "gold standard" but this may not be feasible from a practical and ethical point of view.[15 18 25] Consequently, to evaluate the impact of IFN therapy on survival and development of clinical complications in HCV related cirrhosis, we decided to perform a non-randomised prospective controlled trial. Patients in our study population were homogeneous in terms of recruitment criteria, stage of liver disease at entry, follow up (all patients being recruited and evaluated in the same department), and treatment (all treated patients receiving the same type of IFN for 12 months, if tolerated, and no patient receiving any adjunctive treatment at enrolment). Although the study was not randomised, we tried to minimise susceptibility and selection biases by excluding alcoholic patients and by matching members of the comparison group according to potentially confounding variables.[26] Despite this, some baseline characteristics in the two groups (serum ALT, α fetoprotein levels, platelet number, and oesophageal varices) proved not to be similar (table 1). However, based on the results of multivariate analyses identifying the independent predictive factors for clinical complications, such differences should not have significantly affected our results. In fact, among unevenly distributed variables, only α fetoprotein ⩾20 ng/ml and the presence of oesophageal varices proved to be independent

Table 4 Univariate analysis of risk factors for hepatocellular carcinoma (HCC)

	HCC (n=25)	*No HCC (n=119)*	*p Value*
Mean age (y)	59.3 (6.6)	57.7 (7.7)	NS
Sex (M/F)	13/12	53/66	NS.
ALT (IU/l)	106.9 (66.7)	120.7 (77.1)	NS
Platelets (×1000/mm^3)	105.8 (57.6)	128.5 (61.3)	NS
Albumin (g/dl)	3.6 (0.4)	3.8 (0.4)	0.014
Prothrombin activity (%)	72.5 (13.6)	77.9 (13.1)	0.049
Bilirubin (mg/dl)	1.2 (0.5)	1.1 (0.6)	NS
Alkaline phosphatase (IU/l)	276.2 (101)	247.7 (93.2)	NS
γ-Glutamyltransferase (IU/l)	83.6 (48.8)	68.1 (52.4)	NS
α-Fetoprotein (n (%))			
< 20 ng/ml	15 (60)	95 (80)	0.02
⩾20 ng/ml	10 (40)	24 (20)	
Oesophageal varices (n (%))			
0	7 (28)	60 (50)	
F1	11 (44)	49 (41)	0.0047
F2/F3	7 (28)	10 (9)	
IFN treatment (n (%))			
Yes	6 (24)	66 (55.5)	0.018
No	19 (76)	53 (44.5)	

Values are mean (SD) or number (%).
Normal values: alanine aminotransferase (ALT) <40 IU/l, alkaline phosphatase <280 IU/l, γ-glutamyltransferase <50 IU/l.

Table 5 Adjusted relative risk of hepatocellular carcinoma (HCC) in 72 patients treated with interferon (IFN) and 72 untreated controls

Variable	*Code*	*β*	*SE*	*p Value*	*Odds ratio*	*95% CI*
IFN therapy	0: No					
	1: Yes	1.47	0.49	0.002	4.3	1.6–11.4
Size of varices	0: Absent					
	1: F1	0.98	0.32	0.002	2.6	1.4–5.0
	2: F2/F3					
α Fetoprotein	0: <20 ng/ml					
	1: ⩾20 ng/ml	1.57	0.45	0.0005	4.8	1.9–11.8

Model χ^2=27.13 with 6 df, p<0.0001. Adjusted for baseline prothrombin time, albumin levels, and duration of follow up.
SE, standard error.

predictors for the development of hepatocellular carcinoma. Thus the higher risk for untreated patients deriving from their higher prevalence of oesophageal varices should have been somewhat balanced by the higher prevalence of α fetoprotein ⩾20 ng/ml found in treated patients. Finally, to examine for potentially confounding factors, we used multivariate statistical techniques in the data analysis.

The IFN treatment schedule used in this study does not comply with currently available guidelines.[27 28] However, it should be kept in mind that this study started in 1992 when no established experience in treating cirrhotic patients was available. Therefore, we chose an escalating schedule to minimise potential hazards due to IFN induced side effects. Despite this, the success rate of treatment closely matched that obtained using treatments complying with current guidelines. In fact, administration of IFN induced a sustained biochemical response in 10% of patients and was well tolerated. These results are in line with a recent combined analysis of several large studies performed in patients with HCV related cirrhosis, which achieved a sustained biochemical response in 9% of cases.[29]

Our study shows that the natural history of cirrhosis was not significantly affected by IFN treatment as both overall and event free survival did not differ between treated and untreated patients. However, it should be noted that none of the patients who achieved a sustained response with IFN treatment died or experienced any complications. As far as the prognostic factors are concerned, the laboratory parameters of Child-Pugh score at baseline (albumin, bilirubin, and prothrombin activity) were found to be independent prognostic factors for clinical complications.

The finding that IFN therapy was not associated with improvement in survival or event free survival is in agreement with the results of Valla and colleagues[14] and with those of the Eurohep retrospective multicentre analysis.[16] In contrast, they differ from those of other reports.[10 11 13] Potential biases in individual studies could explain these discrepancies. It is worth noting that in some studies, age and sex distribution of treated and untreated patients were not homogeneous, and this could influence outcome.[25] Moreover, in retrospective studies, disease severity could have influenced eligibility for IFN treatment while we used disease severity, as assessed by the Child-Pugh score, as a means of matching treated and untreated patients.

An important finding in the present study was the significant reduction in the cumulative incidence of hepatocellular carcinoma in IFN treated patients compared with untreated patients. The association between IFN treatment and development of hepatocellular carcinoma was also confirmed by the multivariate analysis which showed that the absence of IFN treatment was an independent factor associated with development of hepatocellular carcinoma. The impact of IFN therapy was even more evident in patients achieving a sustained response, as reported by others.[6 12 15] These results seem to contrast with our previous retrospective analysis[5] which reported a 20% cumulative incidence of hepatocellular carcinoma in patients treated with IFN after five years of follow up. This discrepancy could be ascribed not only to the uncontrolled nature of that study but also to the lower dose of IFN administered. Interestingly, in the present study, all hepatocellular carcinomas were observed in NRs or TRs receiving a low or medium cumulative IFN dose. These observations suggest that patients receiving high doses of IFN and/or showing sustained normalisation of ALT levels during follow up significantly reduced their risk of developing hepatocellular carcinoma.

An interesting finding of our study was the observation that by stratified analysis, IFN proved to be mainly effective in patients with basal α fetoprotein serum levels ⩾20 ng/ml, who can be considered an extremely high risk group for developing hepatocellular carcinoma.[30 31] In fact, our data showed that after five years of follow up, the cumulative incidence of hepatocellular carcinoma in patients with basal α fetoprotein serum levels ⩾20 ng/ml was 17% among treated and 66% in untreated patients. Considering the difficulties in planning and conducting a randomised clinical trial, as stated above, these data suggest that a prospective trial aimed at assessing the efficacy of IFN in preventing hepatocellular carcinoma might be conducted in a selected population of high risk patients.

In conclusion, our study showed that IFN treatment did not seem to affect overall or event free survival of patients with HCV related cirrhosis while it seemed to prevent or delay the development of hepatocellular carcinoma. It must be pointed out however that all patients who achieved a sustained response survived and did not develop any complications during follow up.

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