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Natural course of treated and untreated chronic HCV infection: results of the nationwide *Hepnet.Greece* cohort study

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SUMMARY

Background
Interferon (IFN-α)-based regimens have been used with varying success in the treatment of chronic hepatitis C (CHC) for over two decades. The effect of such treatments on the natural course of CHC has been evaluated in small clinical trials with conflicting results.

Aim
To investigate the natural course of IFNα-based -treated and untreated patients with CHC by analysing data from the HEPNET.GREECE study.

Methods
We retrospectively analysed 1738 patients from 25 Greek Centres (median age 40.1; males 57.6%; cirrhosis 9.2%), 734 untreated and 993 treated with IFNα-based regimens [44.7% sustained viral response (SVR)], followed-up for median 25.2 and 46.8 months, respectively.

Results
During follow-up, 48 patients developed liver decompensation and 24 HCC. Older age was significantly related to disease progression (HR = 2.6 per 10 years of increasing age). Stratified by baseline cirrhosis, Cox analysis showed that patients with SVR, but not without SVR, had significantly lower hazard for events compared with nontreated patients (HR = 0.16; $P < 0.001$), whereas the detrimental effect of older age remained highly significant. Separate group analysis demonstrated that in cirrhosis, the beneficial effect of treatment was evident even without SVR. Treatment effect interacted significantly with age, indicating that older patients, mainly noncirrhotic, gained the most benefit.

Conclusions
IFNα-based treatment does alter the natural course of CHC. A protective effect is mostly present in patients with SVR, but older patients, at higher risk of events, gain the greatest benefit. In established cirrhosis, treatment carries a protective effect even among those without SVR.

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BACKGROUND

Hepatitis C (HCV) infection is an important public health issue. An estimated 170 million persons are chronically infected with HCV worldwide,[1] while in the general population of Greece, HCV prevalence approximates 1–1.9%.[2, 3] Chronic hepatitis C (CHC) has a variable course.[4, 5] Although 20–25% of CHC infected patients maintain persistently normal serum aminotransferases and experience relatively slow histological progression,[6, 7] other patients present a more active biochemical course.[8] Overall, 30% of the CHC patients may progress to cirrhosis in their lifetime,[8] whereas 3–8% of cirrhotic patients may develop hepatocellular carcinoma (HCC) every year.[9–11]

During the last two decades, standard and pegylated interferon alpha (IFNα), alone or in combination with ribavirin, has been used in the treatment of CHC with varying success. The effect of such treatments on the natural course of CHC has been evaluated in small clinical trials with conflicting results.[12–14] While treatment-induced sustained virological response in histologically mild CHC has been associated with a significantly better clinical outcome, it remains unclear whether the beneficial effects of treatment persist among nonsustained responders as well[11, 15–18] or even among those with advanced fibrosis or cirrhosis.[19, 20]

For the last 5 years, we have conducted a nationwide Greek study collecting data on hepatitis C from 25 Hepatology Centres throughout the country. As a large percentage of cases had remained untreated for a considerable period of time, we compared their natural course with that of patients having received interferon-based therapy. As our study included a broad patient population (patients with various sources of infection; wide range of ages; varying disease stages) and a large number of patients, it provided us with the opportunity to study the natural history and the effect of treatment on both cirrhotic and noncirrhotic patients adjusting for other potential confounders.

PATIENTS AND METHODS

In 2003, the HEPNET.GREECE network was established with the support of the Hellenic Center for Infectious Disease Control and Prevention (KEELPNO) aiming to collect and evaluate data on patients with CHC in Greece. Twenty five Centres throughout the country participate in the network. Eligible for enrolment were all patients with CHC (positive anti-HCV and detectable serum HCV RNA), who where under follow-up on 1 January 1997, independently of treatment and final clinical outcome or patients who initiated their follow-up at the participating centres during the period from 1 January 1997 till the end of June 2006. Patients must have been followed up at the same centre for at least 12 months or should have been under follow-up up until June 2006.

The study protocol was reviewed and approved by the Governing Board of KEELPNO.

A structured case report form (CRF) covering demographic, biochemical, virological, serological, histological information, as well as a detailed therapy history and the clinical status of the patients was built up for data collection. Prior to the network establishment (i.e. before 2003), data were collected retrospectively from the patients' medical records and prospectively updated twice per year thereafter. All case report forms were submitted to a Statistical and Data Management Center based in the Department of Hygiene and Epidemiology of the Athens University School of Medicine. After 2005, data have been recorded electronically, the program automatically prohibiting submission, if important information was missing. For this report, all data collected through CRFs were analysed.

Excluded from the current analysis were patients co-infected with the hepatitis B virus (HBV) or the human immunodeficiency virus (HIV), patients aged less than 14 years at study entry, those followed up for less than 1 year in the same clinic and patients having experienced an event (defined below) prior to the entry in the study.

Entry into the study was defined as the date of the first visit to the clinic of the respective participating Centre. Follow-up was considered the time interval between the study entry and the last available clinical information or until June 2006. Analysis time was the time interval between the study entry and the diagnosis of a clinical event or the end of follow-up in the absence of an event. A primary endpoint or clinical event was defined as the development of liver decompensation, HCC, transplantation or liver-related death, whichever came first. Sustained biochemical (SBR) or virological response (SVR) was evaluated at 6 months after the end of the last treatment course. The subset of patients still on treatment on June 2006 or with a follow-up time after ending treatment of less than 6 months were considered as untreated with their follow-up time censored at treatment initiation.

The diagnosis of cirrhosis was histological (stage 6, according to Ishak *et al.*).[21] In a minority of patients lacking a baseline liver biopsy, the presence of cirrhosis at study entry was made by a consensus of evidence provided by haematological findings compatible with hypersplenism or by endoscopy (portal gastropathy and/or oesophageal or fundal varices) and pertinent ultrasound findings.[22]

For the subset of patients who were infected through intravenous drug use (IVDU) or by blood transfusion (Tx), the duration of HCV infection was estimated as the time interval between the last available information and the date of first intravenous drug use or blood transfusion (provided that it was prior to 1992). For HCV-RNA determination, commercially available methods were employed in 94.0% of the patients (12.2% qualitative; 87.8% quantitative PCR), 2.8% bDNA and 3.2% by other assays.

Statistical analysis

Comparison of categorical variables was performed by the chi-square test or by the Fisher's exact test, as appropriate. For the comparison of continuous variables in subgroups of the study population, the nonparametric Mann–Whitney test was used. The effect of prognostic factors on the time to clinical progression was analysed using Cox proportional hazard models, stratified by baseline cirrhosis. Sensitivity analyses using separate Cox proportional hazard models for each group and treating therapy as a time-varying cofactor were also performed. Kaplan–Meier survival curves were used to estimate the effect of virological and biochemical response to therapy on clinical events whereas groups were compared by long-rank test.

RESULTS

Description of the study population

By June 2006, 3020 subjects with CHC had been enrolled into the HEPNET.GREECE study. Excluded were 143 HBV co-infected patients, 66 younger than 14 years of age at study entry, 54 subjects who had experienced a clinical event prior to study entry, seven patients in whom the cirrhosis status could not be evaluated and 1012 with a follow-up of less than 1 year. Those excluded due to a limited follow-up, were marginally more males (61.4% vs. 57.5%, $P = 0.050$), but comparable with those included, in terms of age, platelet counts total bilirubin levels, HCV genotypes and presence or absence of cirrhosis. Their group included, more IVDU (38.1% vs. 28.3%, $P < 0.001$) with shorter duration of HCV infection (median 15 vs. 19 years, $P < 0.001$) and fewer patients with elevated ALT (70.4% vs. 77.7%, $P < 0.001$) or diabetes (4.5% vs. 6.7%, $P = 0.019$). The evaluable population, therefore, consisted of 1738 patients.

A liver biopsy permitting histological evaluation of the disease stage was available in 1138 (65.5%) of the 1738 cases. Histological evidence of cirrhosis was present in 131 (11.5%) of them. In 29 (4.8%) of 600 patients without a liver biopsy, the diagnosis of cirrhosis was made on clinical/laboratory grounds, making a total of 160 patients (9.2%) with cirrhosis in the entire study group.

Table 1 shows the baseline characteristics of the study population for all patients and for those with or without evidence of cirrhosis. The median age was 40.1 years, whereas 26.9% of the patients were aged above 55 years. The corresponding figures for cirrhotic and noncirrhotic patients were 57.0 years (55.6%) and 38.7 years (23.8%) respectively. In general, cirrhotic patients tended to be older, with longer duration of HCV infection, being overweighed, suffering from diabetes mellitus, having elevated ALT and being infected with genotype 1, than noncirrhotic patients. There were no significant differences between the two groups by gender and ethnicity.

Overall, patients had been followed up for a median (interquartile range, IQR) time of 3.2 (1.9–6.0) years, being 2.5 (1.7–4.6) for cirrhotics and 3.3 (1.9–6.2) years for noncirrhotics at study entry.

Of the 1727 patients with available treatment information, 993 (57.5%) had received one or more IFNα-related courses and 734 had not received any treatment. The follow-up time was longer for treated patients than for untreated patients (median 2.1 vs. 3.9 years, $P < 0.001$). Overall, untreated patients were significantly younger (median 37.6 vs. 42.9 years, $P = 0.001$) had shorter estimated duration of infection (median 18.8 vs. 20.3 years, $P = 0.015$) and more frequently normal ALT (33.7% vs. 14.0%, $P < 0.001$) than treated patients. There was no significant difference in the other baseline characteristics including presence of cirrhosis or abnormal values of serum bilirubin, albumin, prothrombin time or platelet counts. Untreated noncirrhotic patients at study entry were significantly younger (36.4 vs. 41.7 years, $P = 0.001$), had shorter estimated duration of infection (18.2 years vs. 19.8,

Table 1. Baseline characteristics of the study population in all patients and in those with or without evidence of cirrhosis at study entry

		Cirrhosis at entry		
	All patients (N = 1738)	No (n = 1578)	Yes (n = 160)	P-value*
Age at HCV study entry	N = 1712	n = 1555	n = 157	<0.001
Median (IQR)†	40.1 (30.1–55.8)	38.7 (29.4–53.9)	57.0 (44.2–65.5)	
Gender				
Males (n, %)	1001 (57.6)	917 (58.1)	84 (52.5)	0.171
Females (n, %)	737 (42.4)	661 (41.9)	76 (47.5)	
Ethnicity	N = 1492	n = 1349	n = 143	0.877
Greek (n, %)	1269 (85.1)	1148 (85.1)	121 (84.6)	
Infection source	N = 1738	n = 1578	n = 160	<0.001
IVDU‡ (n, %)	494 (28.4)	471 (29.9)	23 (14.4)	
Transfusion (n, %)	442 (25.4)	397 (25.2)	45 (28.1)	
Other (n, %)	186 (10.7)	177 (11.2)	9 (5.6)	
Unknown (n, %)	616 (35.4)	533 (33.8)	83 (51.9)	
Estimated duration of infection (years)	N = 890	n = 824	n = 66	<0.001
Median (IQR)†	19.4 (12.8–27.9)	18.9 (12.4–27.5)	23.9 (18.4–32.2)	
BMI (kg/m^2) at baseline	N = 1131	n = 1034	n = 97	0.019
≤ 25 (n, %)	547 (48.4)	512 (49.5)	35 (36.1)	
25–30 (n, %)	447 (39.5)	396 (38.3)	51 (52.6)	
>30 (n, %)	137 (12.1)	126 (12.2)	11 (11.3)	
Diabetes mellitus at 1st visit	N = 1738	n = 1578	n = 160	<0.001
Yes (n, %)	116 (6.7)	90 (5.7)	26 (16.3)	
Genotype	N = 1218	n = 1111	n = 107	0.003
1 (n, %)	563 (46.2)	498 (44.8)	65 (60.8)	
2,3 (n, %)	490 (40.2)	463 (41.7)	27 (25.2)	
4 (n, %)	165 (13.6)	150 (13.5)	15 (14.0)	
ALT	N = 1315	n = 1182	n = 133	0.001
Elevated§ (n, %)	1022 (77.7)	904 (76.5)	118 (88.7)	
Normal (n, %)	293 (22.3)	278 (23.5)	15 (11.3)	
Total bilirubin	N = 1058	n = 938	n = 120	<0.001
≥1.2 mg/dL (n, %)	161 (15.2)	125 (13.1)	36 (30.0)	
<1.2 mg/dL (n, %)	897 (84.8)	813 (86.7)	84 (70.0)	
Albumin (g/dL)	N = 936	N = 833	N = 103	0.001
<3.5 (n, %)	21 (2.2)	13 (1.6)	7 (7.8)	
≥3.5 (n, %)	915 (97.8)	820 (98.4)	95 (92.2)	

Information for the presence or absence of cirrhosis was not available in 7 of the 1745 patients.
* Comparing cirrhotic with noncirrhotic patients.
† Interquartile Range (IQR).
‡ Intravenous drug use.
§ Higher than the upper normal limit used or higher that 40 IU/L if the upper normal limit is missing.

P = 0.018) and less frequently elevated ALT (64.9% vs. 85.5%, P < 0.001) than treated subjects. Among cirrhotics at study entry, there was no difference in terms of age, presence of diabetes, elevated ALT, albumin, prothrombin time or platelet counts between treated subjects and untreated subjects. Treated cirrhotic patients were more likely to be overweighed and have low bilirubin values than untreated ones.

Treatment data for all patients and for those with and without cirrhosis at study entry are shown in Table 2. Most patients (748, 75.3%) received only one treatment course, 177 (17.8%) two courses and 68

Table 2. Treatment history of all patients and those with or without evidence of cirrhosis at study entry

		Cirrhosis		
	All patients $N = 1727$	No $N = 1570$	Yes $N = 157$	P-value
Anti-viral therapy				
No	734 (42.5)	677 (43.1)	57 (36.3)	0.100
Yes	993 (57.5)	893 (56.9)	100 (63.7)	
Type of most recent regimen				
IFNα*	299 (30.1)	266 (29.8)	33 (33.0)	0.092
IFNα + RIB†	257 (25.9)	227 (25.4)	30 (30.0)	
Peg-IFNα‡	34 (3.4)	28 (3.1)	6 (6.0)	
Peg-IFNα+RIB	403 (40.6)	372 (41.7)	31 (31.0)	
Treatment courses				
1	748 (75.3)	677 (75.8)	71 (71.0)	0.505
2	177 (17.8)	155 (17.4)	22 (22.0)	
≥3	68 (6.9)	61 (6.8)	7 (7.0)	
Virological response				
No response	384 (38.7)	328 (36.7)	56 (56.0)	<0.001
Relapse	165 (16.6)	148 (16.6)	17 (17.0)	
SVR§	444 (44.7)	417 (46.7)	27 (27.0)	
Biochemical response				
No response	287 (28.9)	238 (26.7)	49 (49.0)	<0.001
Relapse	242 (24.4)	223 (25.0)	19 (19.0)	
SBR¶	464 (46.7)	432 (48.4)	32 (32.0)	

Information on the treatment history and/or presence of cirrhosis was not available in 18 of the 1745 patients.
* Recombinant alpha interferon.
† Ribavirin.
‡ Pegylated alpha interferon.
§ Sustained virological response.
¶ Sustained biochemical response.

(6.9%) more than two. In total, 384 (38.7%) patients had virological nonresponse, 165 (16.6%) virological relapse and 446 (44.76%) SVR, while 287 (28.9%) patients had biochemical nonresponse, 242 (24.4%) biochemical relapse and 464 (46.7%) SBR. As expected, virological and biochemical response rates were significantly higher in patients without cirrhosis (46.7% and 48.4%, respectively) compared with patients with cirrhosis (27.0% and 32.0% respectively).

Clinical events

During follow-up, 72 (4.1%) clinical events were observed. The first diagnosis of clinical progression was liver decompensation in 48 and HCC in 24 cases, leading to 5 liver-related deaths. Another 15 patients died of non liver-related causes (IVDU overdose 4; stroke 4; car accident 3, other causes 4). These cases were not considered as part of the primary outcome. However, sensitivity analysis accounting these cases in the primary outcome showed that all main results presented in this section persisted, although reported differences were slightly diluted because nonspecific events were added in the clinical outcome. None of the patients underwent a liver transplantation before the diagnosis of an end-point event. Forty two of the 72 clinical events were observed in noncirrhotic patients (representing 2.66% of the total number of them) and 30 in cirrhotic patients (18.75%). The overall incidence rate was 8.7 (95% CI: 6.9–10.9) per 1000 person-years, being 59.0 (95% CI: 41.2–84.3) and 5.4 (95% CI: 4.0–7.3) in patients with and without cirrhosis respectively.

The univariate effect of various factors on the risk of developing an event is shown in Table 3. Results are based on Cox proportional hazard models, stratified by baseline cirrhosis. Statistically or marginally significant factors were gender, age at study entry,

Table 3. Prognostic factors of HCV clinical progression. Results from stratified by cirrhosis at study entry univariate Cox proportional hazard models

Factor	HR*	95% CI*	*P*-value
Gender (Female vs. Male)	1.578	(0.981–2.539)	0.060
BMI (kg/m^2) at baseline			
25–30 vs. ≤ 25	0.907	(0.444–1.851)	0.789
>30 vs. ≤ 25	1.008	(0.359–2.830)	0.988
Diabetes at 1st visit (Yes vs. No)	1.470	(0.777–2.782)	0.237
Infection source			
Transfusion vs. IVDU†	5.486	(1.277–23.573)	0.022
Other vs. IVDU	6.276	(1.265–31.147)	0.025
Unknown vs. IVDU	8.813	(2.115–36.717)	0.003
Genotype			
Type 2,3/Type 1	0.444	(0.167–1.180)	0.104
Type 4/Type 1	0.743	(0.255–2.162)	0.586
Age at study entry: per 10 years increase	2.634	(2.091–3.318)	<0.001
Estimated duration of infection: per 10 years increase	1.057	(0.716–1.560)	0.781
IFNα-based therapy: Yes/No	0.433	(0.269–0.697)	0.001
Virological response			
No response/no therapy	0.621	(0.367–1.049)	0.075
Relapse/no therapy	0.503	(0.197–1.289)	0.152
SVR/no therapy	0.162	(0.063–0.416)	<0.001
Biochemical response			
No response/no therapy	0.756	(0.440–1.298)	0.310
Relapse/no therapy	0.429	(0.190–0.966)	0.041
SBR/no therapy	0.148	(0.058–0.380)	<0.001

* HR: hazard ratio; 95% CI: 95% confidence interval.
† Intravenous drug use.

source of HCV infection and IFNα-based therapy, with women, those infected through another than IVDU route and older persons having higher hazard to experience a clinical event.

Overall, IFNα-based therapy significantly decreased the probability of developing an event. Among treated patients, those having experienced SVR (and/or SBR) had the lowest hazard of developing a clinical event. In fact, there was no statistically significant difference between nonresponders and relapsers. Sensitivity analysis treating treatment response as a time-varying variable showed similar results. Due to the limited follow-up time, the rate of disease progression was low particularly for noncirrhotics at study entry. Only one person from the noncirrhotics and four from cirrhotics with SVR had developed a clinical event. Most events had occurred among untreated or those with treatment failure (22 and 18 respectively for noncirrhotics and 15 and 7 for cirrhotics). Although the limited number of events did not allow us an in depth analysis for cirrhotic and noncirrhotic subjects separately, such analysis was attempted in an effort to investigate possible differential treatment effects by group. A treatment effect was evident in both groups. The main difference was that while noncirrhotic nonresponders and relapsers did not differ significantly from the untreated, in patients with cirrhosis, treatment seemed to have a significant effect (Figure 1).

In the multivariate analysis, gender and source of HCV infection did not persist as significant variables. Apparently, their effect was confounded by the effect of age at study entry as women and those infected through another than IVDU mode were significantly older in the study population (data not shown). Results from the stratified multivariate Cox proportional hazards models showed that patients with SVR had significantly lower hazard of developing a clinical event compared with nontreated patients (Table 4). The beneficial effect of treatment was evident even among nonSVR patients, although the difference with untreated patients was not statistically significant at the nominal statistical level and the magnitude of the

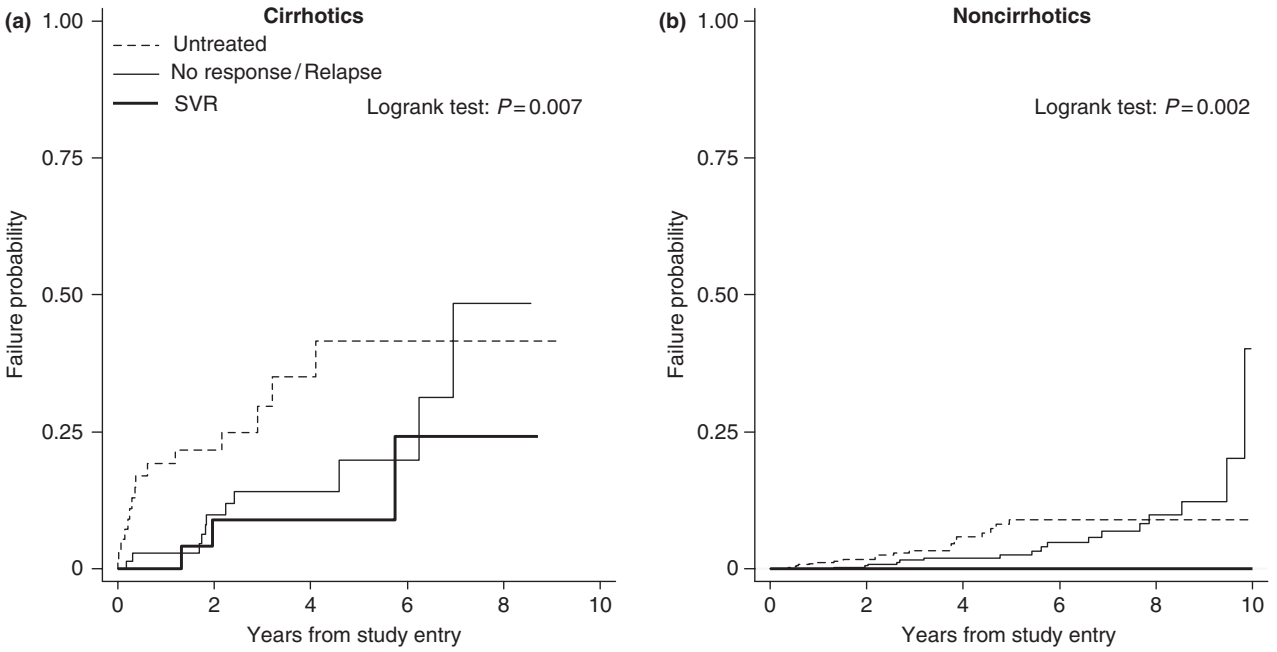

Figure 1. Cumulative failure probabilities by treatment and virological response for patients with and without evidence of cirrhosis at study entry.

Table 4. Prognostic factors of HCV clinical progression. Results from stratified by cirrhosis at study entry multivariate Cox proportional hazard models

Model	HR	95% CI	*P*-value
Virological response			
Age at entry per 10 years increase	2.419	(1.939–3.017)	<0.001
Virological response			
No response/no therapy	0.602	(0.357–1.014)	0.056
Relapse/no therapy	0.531	(0.206–1.369)	0.190
SVR/no therapy	0.240	(0.091–0.633)	0.004
Biochemical response			
Age at entry per 10 years increase	2.440	(1.956–3.043)	<0.001
Biochemical response			
No response/no therapy	0.790	(0.462–1.351)	0.389
Relapse/no therapy	0.424	(0.187–0.961)	0.040
SBR/no therapy	0.191	(0.073–0.500)	0.001

effect was almost half of that of SVR patients. The detrimental effect of older age at study entry remained highly significant with about 2.5-fold higher hazard for each 10-year age increase. When considering biochemical instead of virological response, similar results were revealed (Table 4). Sensitivity analysis including also albumin levels at study entry as a covariate showed that results regarding treatment effect remained practically unchanged, although the significance level was increased (particularly in the sub-group analysis when analysing cirrhotics) due to the reduced sample size as albumin was available for about half of the patients.

Further analysis revealed a significant interaction (P = 0.033) between treatment and age at study entry. More specifically, a beneficial effect was observed for treated patients older than 55 years at study entry [HR = 0.29, 95% CI: (0.17–0.50), P < 0.001], but not for treated patients ≤55 years old (P = 0.923). This was particularly evident among noncirrhotics (P for interaction: 0.018), but not among cirrhotics (P for interaction: 0.876). The detrimental effect of age, although present

in both treated and untreated groups, was stronger in the untreated group [HR = 6.24, 95% CI: (2.84–13.72), $P < 0.001$ and HR = 22.51, 95% CI: (8.52–59.52), $P < 0.001$ respectively]. However, the number of events was too small for a further evaluation of the interaction between age and sustained virological response following treatment. Exploratory analysis results showed that the beneficial effect of SVR, although stronger among the older, was present also among younger persons. On the contrary, among treated patients without SVR, the beneficial treatment effect was evident only for the older persons (data not shown).

DISCUSSION

In this large, multicentre, national Greek study involving 993 treated and 734 untreated patients with chronic hepatitis C, it was demonstrated that the most important factor affecting the progression of liver disease was older age at diagnosis and that IFNα-based treatment significantly improved the outcome of the disease. Patients with SVR had the best clinical outcome compared to untreated patients and the beneficial effect of SVR was present in all patients, irrespective of cirrhosis. Moreover, in patients with cirrhosis, a protective effect of treatment was found even among those without SVR. For patients without cirrhosis, the beneficial effect of IFNα treatment was particularly evident in older patients, that is, in patients with the worst prognosis if left untreated.

Current treatment of chronic hepatitis C achieves high SVR rates, by far higher than those attained by IFNα monotherapy in patients with chronic hepatitis B.[23, 24] In this study, the overall SVR rate was 44.7%, a rate lower than that expected under current treatment in a population with mixed HCV genotypes,[23, 25, 26] but quite high considering that only 40.6% of our treated patients had received pegylated interferon plus ribavirin. The relatively higher rate of SVR in this study can be probably explained by the fact that our studied cohort included considerably less genotype 1 patients (46.2%) and patients with cirrhosis (9.2%), as compared to 62–68% and 12–29% respectively in the three most recent large studies.[23, 25, 26]

Sustained virological response was observed in only 27 (27%) of the 100 treated patients with compensated cirrhosis in our study. Patients with HCV cirrhosis have always been a difficult-to-treat group[27] and SVR in different reported series varies widely between 9.8% and 56%[20, 28, 29] depending on the type (standard IFNα monotherapy vs. pegylated IFNα plus ribavirin) and duration of treatment, as well as HCV genotype composition. The SVR reported in this study closely resembles the overall SVR of 29.6% reported by Veldt *et al.*[20] in their group of 479 cirrhotic patients treated with various interferon-based regimens in a percentage composition approximating our own.

Patients with chronic hepatitis C achieving SVR have significantly lower liver fibrosis and propensity to develop HCC,[12–17, 20] although, in the presence of established cirrhosis, the risk of HCC is not completely eliminated.[30] However, not all treated patents with chronic hepatitis C achieve SVR. In contrast to those patients ending treatment without biochemical and virological response, an appreciable proportion of patients may end treatment with normal ALT and the biochemical quiescence may last weeks or months without a breakthrough, even after virological relapse. The proportion of virological relapsers, although having decreased under current combination therapy, is still present accounting in our study for 165 (16.6%) of our treated cohort or for one in every six treated patients. There is still controversy whether these nonSVR patients gain any benefit of treatment or not[12–14, 31, 32] and the question is further pressing for patients already having had cirrhosis. Our results do support the view that particularly patients with established cirrhosis differ significantly from nontreated patients in the rate of events complicating chronic hepatitis C and that benefit remains for a number of years post-treatment (Figure 1). Indeed, an effect may have been present even among noncirrhotic, nonSVR population, but for this low-event group, a longer follow-up would have been necessary to demonstrate a difference, if present. It was recently shown that prolonged low-dose pegylated IFNα monotherapy does not reduce the progression rate in chronic hepatitis C patients with advanced fibrosis or cirrhosis, who had not had a response to initial treatment with pegylated IFNα and ribavirin[33]. Thus, although according to our data, the first course of anti-viral therapy appears to improve the outcome of cirrhotic patients even if they do not achieve SVR, it seems that there is no way of offering additional benefit in the outcome of nonresponders by long-term, maintenance IFNα based regimens.

The identification in this study of older age as a significant factor accelerating the rate of progression in chronic hepatitis C is in keeping with earlier observations.[8, 34–37] However, an important finding from the analysis of this cohort is the presence of an interaction

between treatment and age at HCV diagnosis, indicating that older patients who respond to treatment have the greatest benefit in terms of decreased probability of events related to progression of liver disease. It is true that older patients do not tolerate interferon treatment well and up to 77% of patients 60 years or older, would discontinue therapy or need dose reduction,[38, 39] limiting the probability of SVR.[39] Although current guidelines do not set an upper age limit for treatment of chronic hepatitis C,[27, 40] to date, most physicians, considering the above problems, avoid treating chronic hepatitis C in older patients. Our data, however, show that treatment should be equally offered to older patients, as they are expected to have the greatest benefit of it, provided they do not have any specific contraindication.[37, 41]

Main limitation of this study was its retrospective, not randomized nature. First, the reasons for the lack of treatment in the untreated group cannot be determined. Second, there is always a reasonable doubt for the comparability between untreated and treated patients. In this study, however, no differences were present in synthetic liver function (serum albumin and bilirubin levels, prothrombin time) and platelet counts between treated and untreated, cirrhotic or non-cirrhotic patients, confirming comparability of the extent of underlying liver disease. In fact, untreated patients were younger and had shorter estimated duration of infection than treated ones, but our results persisted even after adjusting for these factors. It must be noted also, that both younger age and shorter duration of follow-up were expected to be associated with fewer events. The fact that despite this shortcoming, untreated patients demonstrated worse outcome compared with treated ones further emphasizes the benefit of treatment in chronic hepatitis C.

In summary, in this study, we have shown that IFNα-based treatments alter the natural course of chronic hepatitis C not only, as expected, in sustained virological responders, but also in nonsustained responders with cirrhosis and that treatment should equally be offered to older persons, as these are the ones with the greatest benefit in case they achieve SVR.

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