Long term clinical outcome of chronic hepatitis C patients with sustained virological response to interferon monotherapy

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LIVER

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Background: The key end point for treatment efficacy in chronic hepatitis C is absence of detectable virus at six months after treatment. However, the incidence of clinical events during long term follow up of patients with sustained virological response is still poorly documented and may differ between the Eastern and Western world.
Aims: To assess clinical end points during long term follow up of European patients with a sustained virological response to interferon monotherapy.
Methods: Meta-analysis of individual patient data from eight European protocolled follow up studies of interferon treatment for chronic hepatitis C.
Results: A total of 286 sustained virological responders and 50 biochemical responders (detectable virus but normal alanine aminotransferase levels) were followed up for 59 months. Fifteen sustained virological responders (5.2%) had cirrhosis before treatment and 112 (39%) had genotype 1. The late virological relapse rate after five years of follow up was 4.7% (95% confidence interval (CI) 2.0–7.4) among sustained virological responders; all late relapses occurred within four years after treatment. Among sustained virological responders, the rate of decompensation after five years of follow up was 1.0% (95% CI 0.0–2.3) and none developed hepatocellular carcinoma (HCC). Survival was comparable with the general population, matched for age and sex, the standard mortality ratio being 1.4 (95% CI 0.3–2.5). Clinical outcome of patients with cirrhosis was similar to other sustained virological responders. For biochemical responders, the rates of development of decompensation and HCC during long term follow up were 9.1% (95% CI 0.5–17.7) and 7.1% (95% CI 0–15.0), respectively.
Conclusions: Five year survival of European sustained virological responders was similar to the overall population, matched for age and sex. No HCCs were detected during long term follow up.

Chronic infection with the hepatitis C virus (HCV) can lead to decompensated liver cirrhosis and hepatocellular carcinoma (HCC). However, treatment of hepatitis C is based on surrogate end points, and evaluation of treatment for clinical end points has only slowly been forthcoming due to the slow course of the disease and the small number of clinical events in patients treated for hepatitis C.

Protocolled studies use sustained virological response as the key outcome measure for hepatitis C treatment. This sustained virological response is defined as no detectable HCV-RNA in serum at six months after treatment. The aim of this study was to determine the long term clinical outcome of sustained virological responders who had been treated in protocolled studies.

PATIENTS AND METHODS

Study design

All European centres that had published long term data on patients treated for chronic hepatitis C before 1997 were invited to participate in the protocol and to include patients with response to treatment.

Additional entry criteria were study follow up longer than one year and availability of HCV-RNA data. Nine centres met these criteria. Patients from eight European hepatology units were included in the study.[1–12]

Patient selection

Data from 343 consecutive chronic hepatitis C patients with response to interferon monotherapy were obtained. All patients had participated in protocolled studies (clear cohort or randomised controlled trial). Data were collected on separate case record forms, one per patient, by the local investigator. The case record forms were sent to the coordination centre in Rotterdam where data were entered into a central database. Before the data were entered, they were checked and, in case of doubt, contact was made with the local investigator.

Data recorded

Information was obtained on demographics (date of birth, sex) and on details of treatment (initial dose, duration of treatment, and total dose of interferon). Virological data (genotype, viraemia) and biochemical data (platelet count, bilirubin, albumin, and transaminase levels) were measured in certified laboratories of participating hospitals and added to the case record form by the local investigator. Centrally, results were corrected for local normal values. Results of pre- and post-treatment liver biopsies were recorded using the HAI score for activity and the Knodell score for fibrosis.[13] All centres used polymerase chain reaction (PCR) methods with a detection limit of 100 copies/ml, except for one centre where PCR with a detection limit of 1000 copies/ml was used before 1998. No late virological relapses were reported from

Abbreviations: HCV, hepatitis C virus; RNA, ribonucleic acid; MU, mega unit; IFN, interferon; PCR, polymerase chain reaction; HCC, hepatocellular carcinoma; ALT, alanine aminotransferase

Table 1 Patient characteristics

	Sustained virological responders	Biochemical responders	p Value (Mann Whitney/ χ^2)
No	286	50	
Age (y) (mean (range))	41 (17–72)	45 (23–72)	0.04
Male (n (%))	169 (59)	26 (52)	0.35
Follow up (months) (mean (range))	59 (12–120)	59 (6–96)	0.99
Total dose of interferon (MU) (mean (SD))	550 (283)	469 (290)	0.05
Genotype 1 (n (%))	112 (39)	21 (42)	0.71
Cirrhosis (n (%))	15 (5.2)	11 (22)	0.00

this centre after introduction of a test with a sensitivity of 100 copies/ml.

Follow up data were recorded every six months and included alanine aminotransferase (ALT) levels, HCV-RNA, and the occurrence of clinical events (decompensation, HCC, death).

Patients were considered to have decompensation if they showed any of the following symptoms: ascites, bleeding varices, jaundice, or hepatic encephalopathy. Patients were classified as having developed cirrhosis on the basis of ultrasound (nodular contour, diminished hepatopetal flow, collaterals), serology (platelets <80000, albumin <35 g/l, clotting factors<50%), or liver biopsy. Patients were considered to have HCC if the α fetoprotein level was >400 and ultrasound confirmed a focal lesion, or if biopsy proved so. Death was classified as liver related or liver unrelated.

Sustained virological response was defined as no detectable HCV-RNA at the end of treatment and after six months of follow up. Patients with normal ALT levels at these time points, but with detectable HCV-RNA at the end of treatment or six months thereafter, were referred to as biochemical responders. Sustained virological responders were considered to have a late virological relapse if HCV-RNA was detectable on any occasion after six months of follow up, confirmed by either a second PCR or elevation of ALT levels above the upper limit of normal.

Statistical analysis

To evaluate factors of influence on late virological relapse, univariate and multivariate Cox regression analyses were performed. The Kaplan-Meier method was used to evaluate the five year late relapse rate and to determine the rate of occurrence of clinical events during five years of follow up. The number of expected deaths and the expected survival probability were calculated based on sex and age ranked mortality among the Dutch general population, which is similar to most European countries.[14] The standard mortality ratio was calculated by dividing the observed number of deaths by the expected number of deaths.

We used multiple regression analysis to identify risk factors for fibrosis progression.

Statistical analyses were performed using SPSS for Windows (SPSS Inc, Chicago, Illinois, USA). All analyses were performed by the Meta-Analysis of Individual Data group in Rotterdam (BEH, SWS, BJV), which is experienced in the conduct of such studies.

RESULTS

Study population

Data were obtained for 343 patients treated for chronic hepatitis C. A total of 286 patients had a sustained virological response and 50 had a biochemical response. Seven patients did not fit the entry criterion of HCV-RNA data availability at the end of treatment and after six months of follow up and were excluded from further analysis.

Characteristics of sustained virological responders and biochemical responders are shown in table 1. Patients had been treated with recombinant interferon a2a, a2b, or natural interferon monotherapy. Patients were treated for an average duration of 39 weeks (range 11–96). Patients with genotype 1 were treated longer (mean duration 41 weeks *v*. 38 weeks in other genotypes; p<0.01) and received a higher total dose of interferon (581 mega units (MU) *v* 525 MU in other genotypes; p<0.01, Mann-Whitney U test).

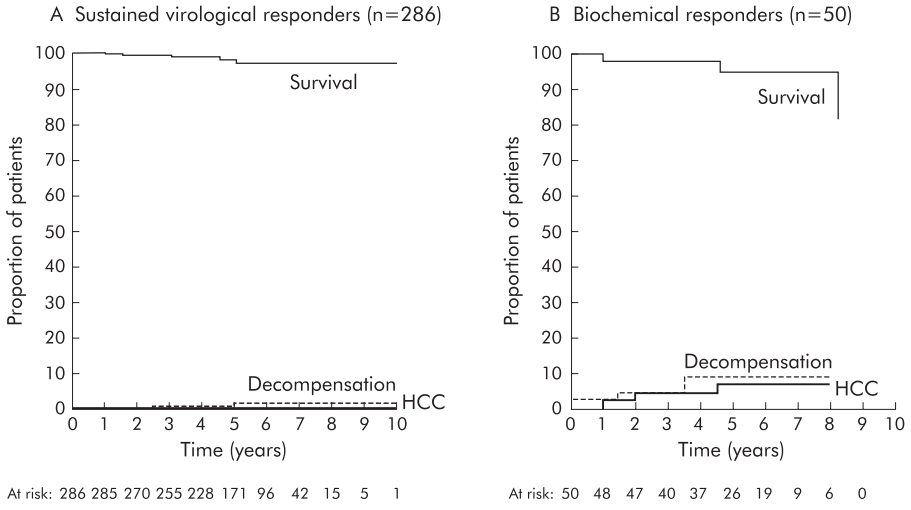

Figure 1 Kaplan-Meier curve showing survival and development of clinical events in sustained virological responders (A) and biochemical responders (B). HCC, hepatocellular carcinoma.

Table 2 Standard mortality ratios (SMR) for sustained virological responders and biochemical responders

	n	Deaths	Deaths expected	SMR	95% CI
Sustained virological responders	286	6	4.3	1.4	0.3–2.5
Biochemical responders	50	3	0.5	5.6	0.0–12.6

95% CI, 95% confidence interval.

Sustained virological responders

Of 286 sustained responders, 15 patients had cirrhosis before the start of treatment, as determined by liver biopsy.

Two patients presented with decompensated cirrhosis after 30 and 60 months of follow up (fig 1). These patients were hepatitis B surface antigen negative and HCV-RNA negative, and no other risk factors for liver disease were reported. The latter patient died of decompensated cirrhosis. Five other patients died of non-liver related causes. One patient died of lung cancer and two patients died of trauma; another patient died of cardiovascular complications and one patient died of a haemolytic uraemic syndrome.

The standard mortality ratio of sustained responders was 1.4 (95% confidence interval (CI) 0.3–2.5) (table 2), and there was no statistically significant difference in mortality between sustained virological responders and the general population, matched for age and sex (fig 2).

Biochemical responders

Fifty patients had normal transaminase levels at the end of follow up and six months after treatment while HCV-RNA was still detectable. Of these biochemical responders, three patients died during long term follow up, all of liver related causes. The occurrence of decompensation and HCC among biochemical responders was 9.1% (95% CI 0.5–17.7) and 7.1% (95% CI 0–15.0), respectively (fig 1). Biochemical responders were older and had a higher prevalence of cirrhosis. Although there was a trend to a higher standard mortality ratio (corrected for age and sex) in biochemical responders after five years of follow up, the difference did not reach statistical significance (table 2).

Liver histology

One hundred and twenty five patients (110 sustained virological responders and 15 biochemical responders) underwent liver biopsy both before and after treatment. Mean time between these two biopsies was 1.6 years (SD 0.8). Thirty two sustained virological responders (29%) and none of the biochemical responders showed regression of fibrosis. Progression of fibrosis was seen in six sustained virological responders (5%) and in three biochemical responders (20%) (table 3). Baseline characteristics of sustained virological responders and biochemical responders who underwent two biopsies were different, with sustained virological responders being younger (mean 39 (SD 13) *v* 47 (14) years), having a lower mean pretreatment fibrosis stage (1.75 (1.1) *v* 2.5 (1.4)), and having a shorter time between the two biopsies (1.5 (0.6) *v* 2.3 (1.5) years). Therefore, we performed a multiple regression analysis to determine independent risk factors for progression of fibrosis. Fibrosis progression was associated with older age, lower pretreatment fibrosis score, and biochemical response rather than sustained virological response (table 4).

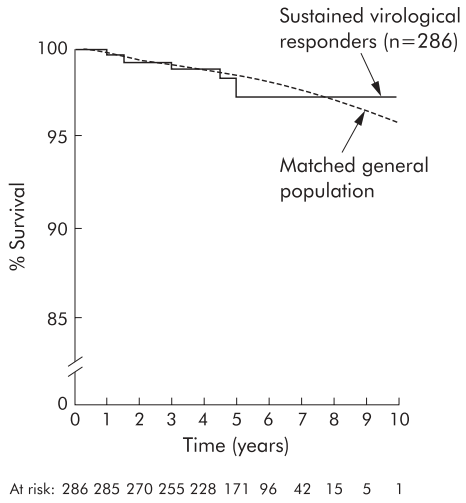

Figure 2 Kaplan-Meier curve showing survival of sustained virological responders compared with the age and sex matched general population.

Late relapsers

Twelve sustained responders had a late virological relapse (fig 3). In six patients (50%), late virological relapse was accompanied by an elevation in transaminase levels. Multivariate Cox regression analysis did not show any pretreatment factors to be associated with an increased risk for late virological relapse. None of the late relapsers developed decompensation or HCC during follow up.

DISCUSSION

This large European study allows, for the first time, an approximation of the incidence of clinical events during long term follow up of sustained virological responders in Europe. The most important finding is that clinical events are rare in this population, indicating that sustained virological responders have an excellent prognosis.

The largest European study to date describing clinical outcome in sustained responders to interferon treatment did not report any events among 74 patients followed up for 2.7 years.[15] Two other European studies, involving seven and 56 sustained responders, also showed no clinical events during 4.6 and 5.2 years of follow up, respectively.[8 16] Bruno *et al* described 32 sustained responders of whom one cirrhotic patient developed HCC.[17] Although another HCC has been reported recently in a Western sustained responder,[18] these cases seem to be rare and limited to patients with cirrhosis. In the present study, no HCCs occurred during long term follow

Table 3 Change in fibrosis according to response to treatment in patients who underwent pretreatment and post-treatment biopsies

	SVR	BR
No of patients	110	15
2 points progression	3 (3%)	1 (7%)
1 point progression	3 (3%)	2 (13%)
No change	72 (65%)	12 (80%)
1 point regression	23 (21%)	0 (0%)
2 points regression	9 (8%)	0 (0%)

SVR, sustained virological responders; BR, biochemical responders.

Table 4 Multiple regression analysis assessing risk factors for fibrosis progression

	Hazard ratio	95% CI Lower	95% CI Upper	p Value
Male sex	0.02	−0.29	0.34	0.86
Age	0.29†	0.00	0.03	0.01
Fibrosis stage pretreatment	−0.50*	−0.52	−0.21	<0.01
Activity score pretreatment	0.09	−0.04	0.12	0.37
Time between biopsies	0.08	−0.12	0.29	0.40
Biochemical response to therapy *v* sustained virological response	0.31‡	0.30	1.49	<0.01

*Higher pretreatment fibrosis stage associated with a smaller chance of fibrosis progression, while older age† and biochemical response‡ were associated with a higher chance of fibrosis progression.

up. According to several large studies, the yearly incidence of HCC among Japanese sustained virological responders still varies between 0.02% and 0.5% per year[19–26]; the difference in the incidence of HCC between East and West apparently persists in conditions without detectable viral replication.

The lowest rates in Japan were reported by Yoshida *et al*, with one HCC among 817 sustained responders during 5.4 years of follow up.[26] The highest incidence of HCC reported among sustained responders in Japan was by Kasahara *et al* who reported five HCCs among 313 sustained virological responders followed up for three years.[22]

Fifteen cirrhotic patients were included in this study. Only two patients with decompensated cirrhosis were reported. Among untreated cirrhotics, occurrence of clinical events of 38% (28% decompensation and 10% HCC) would be expected, according to Fattovich and colleagues.[27] These results suggest, but do not prove, a change in the natural course of chronic hepatitis C. Further studies, including more cirrhotics, will be necessary to investigate the effect of treatment on the natural course of chronic hepatitis C.

In this study, sustained virological response was associated with a decrease in fibrosis score. Similar findings have been reported for sustained responders to pegylated interferon.[28 29] Previous studies have shown that regression of fibrosis can also occur in biochemical responders and non-responders to interferon. In common with our study, sustained virological responders show the highest rate of regression.[30] Because of the large proportion of sustained virological responders that showed regression of fibrosis and the low incidence of clinical events in these patients, in our view, non-cirrhotic patients with a sustained virological response can be regarded as cured.

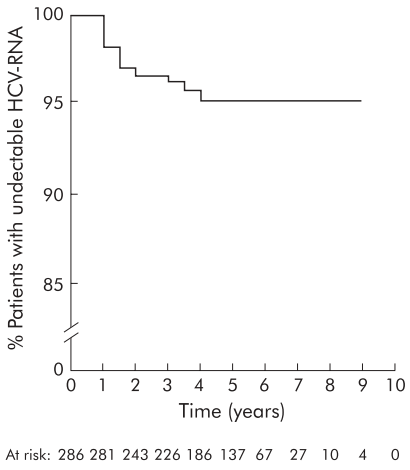

Figure 3 Kaplan-Meier curve showing late virological relapse among sustained virological responders. No late virological relapses were seen after four years of follow up, the maximal delay between the last negative polymerase chain reaction (PCR) and the first positive PCR result being 12 months.

A limitation of our study is that all patients had been treated with interferon monotherapy whereas the current standard therapy for chronic hepatitis C is pegylated interferon with ribavirin. This current standard however dates from 2002 and long term follow up data of peginterferon and ribavirin were not available at the time of this study.[31] In general, combination therapy leads to higher sustained virological response rates[32 33] and also the late relapse rate seems to decrease. In this study with data on interferon monotherapy, the late relapse rate was 4.7% (95% CI 2.0–7.4); Camma *et al* reported 8.7% in a meta-analysis of 14 trials with interferon monotherapy.[34] After four years of follow up of treatment with interferon and ribavirin, late virological relapse rates of 3% (95% CI 1.4–4.6) and 1% (95% CI 0–2.0) have been reported for patients treated for 24 weeks and 48 weeks, respectively.[18] After treatment with pegylated interferon with or without ribavirin, a late relapse rate of 0.8% was reported after four years of follow up.[35] The possibility of reinfection could not be ruled out in our cohort as data on risk behaviour and concordance of genotypes were not available. However, introduction of more sensitive PCR methods may also have contributed to a decrease in late virological relapse over time. It is possible that with an insensitive assay, patients with low viraemia are regarded as sustained virological responders.

As the late relapse rate seems to decrease with newer treatment regimens, long term clinical outcomes may be similar or even better than results obtained with interferon monotherapy. Therefore, in our opinion, the favourable clinical outcome of sustained virological responders is likely to hold true in the era of pegylated interferon and ribavirin.

In conclusion, the long term clinical outcome of patients with a sustained response to interferon is favourable. Five year survival of European sustained virological responders was similar to the general population, matched for age and sex, and no HCCs were detected during long term follow up.

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