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ORIGINAL ARTICLE

How sustained is sustained viral response in patients with hepatitis C virus infection?

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Abstract
Background Sustained virological response (SVR) is achieved in a high proportion of patients with chronic hepatitis C infection, particularly those with genotype 2 or 3 HCV infection. However, data on long-term durability of virological response in patients who achieve SVR are limited.
Aim To evaluate the long-term durability of virological response in patients who have achieved SVR with interferon-based combination therapy.
Methods One hundred patients with chronic HCV infection who had obtained SVR after IFN and ribavirin combination therapy were followed up for up to 8 years with annual HCV RNA testing.
Results During a followed up of 6 months to 8 years, 8 of 100 patients with initial SVR developed late relapse of HCV infection. Relapse was more common in patients who had cirrhosis (5/28 [18%] vs. (3/72 [4%] with no cirrhosis; $p=0.037$).
Conclusion SVR is durable in most patients, but some patients do have late relapse; long term follow up may be particularly important in a subset of patients with HCV infection who have liver cirrhosis.

Keywords Hepatocellular carcinoma · Pegylated interferon · Sustained viral response

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Introduction

Hepatitis C virus (HCV) infection is a major health problem worldwide. Most of the infected persons develop a persistent infection that can progress to chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC).

Currently, pegylated interferon (Peg-IFN) alfa 2a/2b with ribavirin is the standard treatment for chronic HCV infection. Absence of serum HCV RNA 6 months after discontinuation of therapy i.e., sustained virological response (SVR) is generally taken as cure of HCV infection. SVR rates with Peg-IFN-ribavirin treatment are 42–52% of those with genotype 1 HCV infection, and 80% in those with genotype 2 or 3 HCV infection [1]. Successful eradication of HCV is associated with regression of fibrosis and clinical improvement [2, 3].

However, despite treatment, HCV may persist in liver tissues and extrahepatic locations like peripheral blood mononuclear cells (PBMCs) leading to late relapse, defined as reappearance of viremia after SVR has been achieved [4].

Table 1 Baseline characteristics of study subjects (n=100)

Characteristic	Value
Age (mean [SD]) (years)	41.4 [11.0]
Gender (M:F)	78:22
BMI (mean [SD])	26.3 [4.3]
Cirrhosis	28
Alcohol intake	54
Opium intake	11
Diabetes	4
Genotype: 1 / 3/ others[a]	16 / 74 / 10
Liver fibrosis[b] stage 0–2 / 3–4	65 / 7
Type of IFN used: Conventional / pegylated	15/85
Ribavirin dose (mg/kg) (mean [SD])	11.54 (2.17)

[a] Others include one patient with a mixed (genotype 1 and 3) infection and 9 in whom genotype could not be identified

[b] These data were available only for 72 patients

Since, no data are available on long-term clinical outcomes and virological relapse in Indian patients with HCV infection who achieve SVR, [5, 6] we undertook a prospective, long-term follow up study assessing of such patients.

Methods

Patients with chronic hepatitis C who had achieved SVR with antiviral treatment between January 2000 and June 2007, who agreed for follow-up using annual HCV RNA testing, were enrolled in the study. All patients provided written informed consent. The study protocol was approved by our hospital's ethics committee.

Chronic hepatitis C was defined as presence of anti-HCV antibodies (Ortho, Raritan, NJ, or Abott, Chicago, IL, USA), detectable serum HCV RNA (Roche Amplicor; Hoffmann–LaRoche, Basel, Switzerland) and elevated (twice the upper limit of normal) serum alanine aminotransferase (ALT) levels. SVR was defined as undetectable serum HCV RNA levels 6 months after stopping therapy.

The patients underwent a clinical follow-up every 3–6 months for 1 year and yearly thereafter. At each visit, physical examination, hemogram, liver function tests and prothrombin time were done. Patients with ultrasound (US) or histological evidence of cirrhosis were screened for HCC by alpha-fetoprotein measurement every 6 months and ultrasound every year. HCV RNA was tested every year.

Decompensation was defined as development of jaundice, ascites, encephalopathy or variceal bleed. Diagnosis of HCC was based on elevated AFP (>500 pg/mL), space occupying lesion in the liver on US, computed tomogram or magnetic resonance imaging, or / and US-guided FNAC.

Data are expressed as mean (SD). A time-to-event analysis was done using life table method. Fisher's exact test was used to compare proportions. P values below 0.05 were considered significant.

Results

Between January 2000 to June 2007, 128 patients received anti-HCV treatment. Of these, 9 patients did not complete the treatment due to adverse effects (n=4), decompensation of disease (n=1) or financial reasons (n=4). Of the 119 patients who completed treatment, 100 achieved SVR and were followed up. The baseline demographic, clinical, virologic, histologic characteristics and treatment of these 100 patients are shown in Table 1.

All the study patients were negative for HBsAg and anti-HIV. None had decompensated cirrhosis at enrollment, or evidence suggesting HCC on US or serum AFP levels.

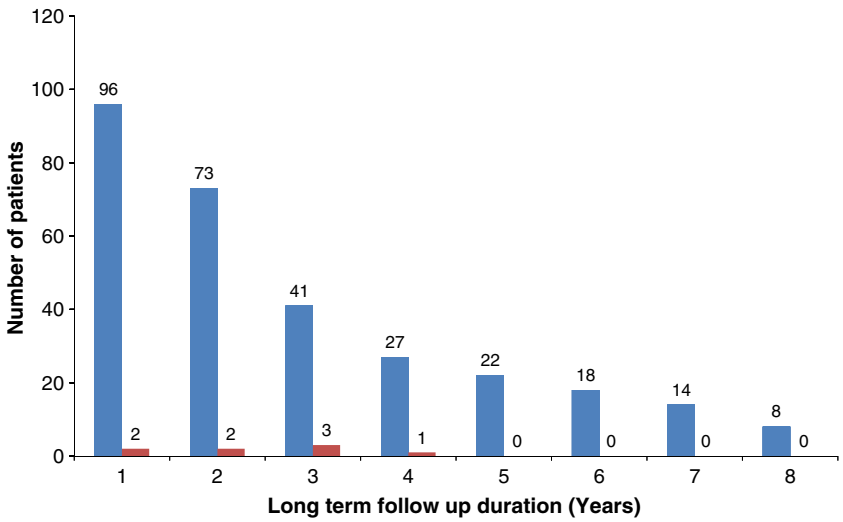

Fig. 1 Long term follow up results

Table 2 Characteristics of patients who had a relapse following sustained virological response

Sr. No	Age	Sex	BMI (kg/m^2)	Alcohol	Genotype	Cirrhosis	Viral load log (IU/mL)	Interferon[a]	Ribavirin dose (mg/kg)	Time to relapse (year)
1	48	M	32.1	Y	3	Y	NA	C	8.88	1st
2	45	M	30.4	N	3	Y	NA	C	10	1st
3	52	M	23.7	Y	3	Y	NA	C	9.38	3rd
4	45	M	21.6	Y	1	Y	3.72	Peg	14.03	2nd
5	52	F	24.6	N	3	N	5.40	Peg	8.84	2nd
6	40	M	28.3	N	3	N	5.39	Peg	8.95	3rd
7	38	F	33.7	N	1	Y	5.71	Peg	14.81	3rd
8	38	M	24.4	Y	3	N	5.80	Peg	10.95	4th

[a] *C* conventional; *Peg* pegylated

Twenty-one patients had US evidence of cirrhosis; of the remaining patients, 72 had undergone pretreatment liver biopsy whereas 7 had refused biopsy. Patients had received either conventional IFN (n=15) or pegylated IFN (n=85) in combination with ribavirin (weight-based); the duration of treatment was 24 weeks for those with genotype 3 HCV infection and 48 weeks for the other patients.

Duration of follow up was 6–96 months. The number of patients completing 1st to 8th year of follow up was 96, 73, 41, 27, 22, 18, 14 and 8, respectively (Fig. 1).

Two patients died during follow up, including one of head injury following a road traffic accident and one of HCC, decompensated cirrhosis, and liver failure. No other patient developed decompensation or HCC.

Eight of 100 patients had virological relapse during follow up, including two each during the first and the second year, three in the third year and one in the fourth year of follow up, and none subsequently. Hence, the cumulative proportion of virological relapses was 0.02, 0.03, 0.07, and 0.04, respectively at 1, 2, 3, 4 years of follow up (Fig. 1).

Clinical, virologic and treatment details of these patients are shown in Table 2. Relapse occurred more often in patients with liver cirrhosis (5/28 [18%]) than in those without cirrhosis (3/72 [4%]; p=0.037), and in those treated with conventional interferon and ribavirin (3/15 [20%]) than in those who had received Peg-IFN and ribavirin (5/85 [6%]; p=0.096) (Table 3). The mean (SD) dose of ribavirin was 10.7 (2.4) mg/kg body weight in those with relapse and 11.6 (2.2) mg/kg in those who maintained remission (p=0.27).

Discussion

This is the first study from India on long-term outcomes of anti-viral therapy for chronic HCV infection. Our study shows that SVR is durable in a majority of patients but late relapses do occur. These relapses occur more commonly in patients with cirrhosis.

The issue of late relapses in hepatitis C infection has been reported earlier [7–11]. A meta-analysis of eight European trials by Veldt et al. reported late relapse rate of 4.7% over 5 year follow up [12]. Similarly, Camma et al. reported 8.7% late relapse in a meta-analysis of 14 trials [13]. The noteworthy limitations of trials included in these meta-analysis were: use of conventional IFN monotherapy, and use of less sensitive diagnostic assays which could have resulted in an over estimate of SVR. The results of durability of SVR after treatment with pegylated IFN and ribavirin were 100% and approximately 99% in two recent studies from western countries [14, 15]. Our study revealed late relapses in 20% patients treated with conventional IFN + ribavirin and 5.9% in those treated with pegylated IFN + ribavirin over 8 year follow up. One reason for high late relapse in our study could be due to presence of poor baseline predictors of response: obesity i.e., BMI >30 (n=3), alcohol intake (n=4) and cirrhosis (n=5). In addition, on retrospective analysis we found that mean dose of ribavirin used in patients treated with conventional IFN was suboptimal as dose reductions were required more frequently in earlier years as erythropoietin use was infrequent.

Table 3 Comparison of relapsers and non-relapsers

	Non-relapsers n=92 (%)	Relapsers n=8 (%)	P
Gender (M)	72 (78.3)	6 (75)	1
Age ≤40	47 (51.1)	3 (37.5)	0.72
BMI ≤30	74 (80.4)	5 (62.5)	1
Alcohol intake	50 (54.3)	4 (50)	1
Opium intake	9 (9.8)	2 (25)	0.21
Cirrhosis	23 (25)	5 (62.5)	0.037
Ribavirin dose ≤12 mg/kg	58 (63)	6 (75)	0.71
Type of IFN: conventional/pegylated	12/80	3/5	0.097
Genotype: 1/3/others	14/68/10	2 / 6 / 0	1

A theoretical explanation for late relapse could be persistence of undetected occult hepatitis C virus in hepatocytes, PBMCs, lymphocytes or macrophages. Earlier studies, possibly using less sensitive assays, have shown that 95% of patients with SVR have no liver HCV RNA 1–2 years after therapy [16]. Another study supporting this reported that clearance of liver HCV RNA was sustained upto 12 years off treatment [17]. However; several recent reports contradict these findings. In a small study, only 2 of 17 patients with SVR remained HCV RNA negative on long term follow up when all body compartments were analyzed [9]. Similarly, in another study viral sequence could be amplified during follow up of 5 years from sera or PBMC in all patients with SVR [18]. More recently, a large cohort of 344 patients followed up for up to 18 years after cessation of treatment, revealed undetectable HCV RNA in serum and PBMCs in all patients, but HCV RNA was detected in 2 of 114 (1.7%) liver biopsies tested [4].

It is known that unlike hepatitis B virus, HCV does not have a latent stage in its replication cycle and cannot integrate into the host genome [4]. Hence, the presence of persistent HCV infection after successful antiviral therapy raises interesting clinical issues like disease progression, hepatocarcinogenesis, reactivation and furthermore, a potential source of HCV spread.

Our study has some limitations. Liver biopsy was not done at follow up in our patients with late relapse; hence it is not possible to comment on occult HCV in liver. Similarly, retesting of genotype/sequencing was not done and a possibility of re-infection cannot be ruled out. Re-infection appears to be unlikely as all the relapses were observed in first 4 years after SVR.

SVR once achieved is sustained in majority of patients. The treating hepatologist need to be aware of occurrence of late relapses in patients with chronic HCV infection with cirrhosis.

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