

Durability of Sustained Virologic Response in Chronic Hepatitis C

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Background/Aims: The aim of this study is to investigate the rate of sustained virologic response (SVR) in chronic hepatitis C patients receiving antiviral treatment. **Methods:** The files of patients with chronic hepatitis C treated with interferon±ribavirin between 1995 and 2009 were reviewed retrospectively. Six months after the end of treatment, patients with negative hepatitis C virus (HCV)-RNA (<50 IU/mL, as determined by the polymerase chain reaction method) were enrolled in the study. **Results:** The mean age of 196 patients (89 males) was 46.13±11.10 years (range, 17 to 73 years). In biopsies, the mean stage was 1.50±0.94; histological activity index was 7.18±2.43. In total, 139 patients received pegylated interferon (IFN)+ribavirin, 21 patients received classical IFN+ribavirin, and 36 patients received IFN alone. The HCV genotypes of 138 patients were checked: 77.5% were genotype 1b, and 22.5% were other genotypes. After achievement of SVR, the median follow-up period was 33.5 months (range, 6 to 112 months), and in this period relapse was only detected in two patients (1.02%) at 18 and 48 months after treatment. **Conclusions:** In total, 98.9% of patients with SVR in chronic hepatitis C demonstrated truly durable responses over the long-term follow-up period of 3 years; relapsed patients had intermittent or low-grade viremia. (**Gut Liver 2013;7:458-461**)

Key Words: Chronic hepatitis C; Interferons

INTRODUCTION

In chronic hepatitis C treatment, the aim is to achieve a sustained virologic response (SVR). The negativity of hepatitis C virus (HCV)-RNA at the end of the therapy and 6 months after the

end of treatment is considered to be a SVR. SVR provides viral eradication in most patients.¹ Interferon monotherapy was the first therapy developed for chronic hepatitis C with SVR levels of <20% for 24 to 48 weeks of administration.^{2,3}

In the last decade, a high rate of eradication and SVR has been achieved with the combination of pegylated interferon (PEG-IFN) and ribavirin.^{4,5} The SVR rate with PEG-IFN and ribavirin combination is 42% to 52% for genotype 1 and 80% for genotype 2 or 3.⁴ The predicting factors which define SVR are patient gender, age at the time of infection, duration of infection, progression of fibrosis, HCV genotype, baseline viral load and rate of decline in viral load during antiviral treatment.⁶⁻⁸ When SVR is achieved, risk of viral relapse is greatly reduced.⁹

The purpose of the study was to investigate the degree of SVR durability through the long term follow-up of chronic hepatitis C patients receiving antiviral treatment.

MATERIALS AND METHODS

1. Patients

Between April 1995 and Oct 2009, 196 chronic hepatitis C patients with SVR were retrospectively enrolled in the study. Among the patients with positive anti-HCV, those patients with detectable HCV-RNA levels and normal or high levels of alanine aminotransferase (ALT) were considered as chronic hepatitis C patients and treated accordingly. Patients with negative HCV-RNA (by polymerase chain reaction) at the end of therapy and at 6 months afterwards were considered as patients with SVR. Anti-HCV was determined by enzyme-linked immunosorbent assay (ELISA) and HCV-RNA was determined by the qualitative Cobas Amplificor HCV Monitor (Roche Diagnostics, Indianapolis, IN, USA) method. The upper limit of ALT was considered

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to be 40 IU/mL. Liver biopsies were evaluated according to the Knodell criteria in terms of histological activity and fibrosis stage.¹⁰ Patients with SVR were followed with HCV-RNA, ALT, and alpha feto-protein levels every 6 months. Patients with no end-of-therapy and month 6 values in the records were not included.

2. Treatment of chronic hepatitis C

Patients received different doses of classical interferon and PEG-IFN. For patients receiving ribavirin, <70 kg received 1,000 mg/day whereas >70 kg received 1,200 mg/day. Durations of treatment ranged between 6 and 18 months.

3. Statistical analysis

The SPSS version 13.0 statistical package program (SPSS Inc., Chicago, IL, USA) was used for the statistical evaluations. Mean±standard deviation (SD) or median was used for the quantitative variables. The differences between groups which were not interdependent were investigated with the nonparametric Mann-Whitney U test. However, the differences between interrelated groups were evaluated with the Wilcoxon test. Correlation analyses were performed by using the Pearson and Spearman correlation tests. The values with a "p-value" of <0.05 were considered as statistically significant.

Table 1. Demographic Characteristics and Laboratory Results of Patients

Characteristic	Value
Age, yr	46.13±11.10 (17-73)
Male/Female	89/107
Cirrhotic/chronic hepatitis	8/191
ALT, IU/mL	101.72±78.84 (12-465)
AST, IU/mL	64.19±43.12 (13-249)
Bilirubin	0.78±0.36 (0.19-2.6)
AFP, ng/mL	4.073±5.43 (0.19-48.67)
Platelets	208,127±72,312 (25,000-451,000)
HCV-RNA, IU/mL	13,869,182±4,472,340 (1,850-27,407,700)
Pretreatment fibrosis stage	
Stage 0-1	89 (64)
Stage 2	24 (17)
Stage 3	20 (15)
Stage 4	5 (4)
Pretreatment HAI	7.18±2.44 (1-18)

Data are presented as mean±SD (range) or number (%). ALT, alanine aminotransferase; AST, aspartate aminotransferase; AFP, alpha feto-protein; HCV, hepatitis C virus; HAI, histological activity index.

RESULTS

1. Baseline characteristic of study subjects

The mean age of 196 patients was 46.13±11.10 years (range, 17 to 73 years), 89 (45%) male and 107 (55%) female. Neither of the genders were considered as statistically significant. Before the treatment, eight patients were at the cirrhotic stage and 188 patients were at the precirrhotic stage. There were 16 patients with chronic renal insufficiency and 17 patients with diabetes mellitus.

Pretreatment demographic and biochemical data for patients as well as fibrosis stages of 138 patients with liver biopsy are shown in Table 1. In liver biopsies, the mean stage was 1.50±0.94 and histological activity index was 7.18±2.43.

2. Distribution of treatment and durability of SVR

A hundred thirty-nine patients received PEG-IFN+ribavirin; 21 patients received classical interferon+ribavirin and 36 patients received classical interferon alone (Table 2). A hundred seventy-nine patients (91%) received treatment for 12 months, 14 patients (7%) for 6 months, and three patients (2%) for 18 months. HCV genotypes of 138 patients were observed: 77.5% was genotype 1b, 5.1% genotype 1a, 9.4% genotype 2, 2a, 2b, 2c, 7.2% genotype 3 and 0.7% genotype 4a.

After achievement of SVR, the mean follow-up period was median 33.5 months (range, 6 to 112 months), and in this period relapse was detected in two patients (1.02%) at 18 and 48 months after treatment. During relapse, HCV-RNA titers of the patients were very low (438 and 6,361 IU/mL) and were found negative for them when repeated. Aminotransferase levels were normal for 96.4% of patients during follow-up. No patients developed complications during the off-drug follow-up period.

The clinical characteristics of two patients who developed relapse were as follows: the first patient was a 43-year-old male patient infected with HCV genotype 1b who received pegylated interferon alpha-2a and ribavirin. Baseline HCV-RNA level was 890,000 IU/mL, fibrosis stage was 2 and histological activity index was 10. The second patient was a 25-year-old male patient infected with HCV genotype 1b who was also treated with pegylated interferon α -2a and ribavirin combination. Baseline HCV-RNA was 6,410 IU/mL, liver fibrosis was found to be minimal and histological activity index was scored 6.

Table 2. Distribution of Treatments for Patients

Treatment	No. (%)
Pegylated interferon+ribavirin	139 (71)
Classical interferon+ribavirin	21 (11)
Classical interferon	36 (18)

DISCUSSION

Regular and long-term follow-up of patients with SVR was not well documented.¹¹ The current study evaluates the long-term results of SVR.

In standard interferon or IFN/ribavirin combination therapies, HCV-RNA was negative for 92% to 100% of patients during the follow-up of 1 to 12 years following SVR in patients with chronic hepatitis C.^{9,12-14} Recent studies reported that cure for HCV infection was achieved with SVR.^{11,15} Additionally, histological improvement was detected in 94% of the patients and persistently normal ALT levels were detected in 93%.¹⁶ Our results also confirmed these data and HCV-RNA level was not detectable in the long term for 99.4% of the patients. ALT was determined to be within normal limits for 153 patients (94%) in the final control.

The available data was relatively less for PEG-IFN/ribavirin combination. In a study by Swain *et al.*,¹⁷ follow-up of 845 patients who achieved SVR with interferon alpha 2a±ribavirin revealed that HCV-RNA was detected in only seven patients (<1%) within 391 to 1,076 days after treatment. For treatments based on PEG-IFN, it was concluded that late relapse was rare after achievement of SVR.¹⁷ More than half (65%) of our patients received PEG-IFN/ribavirin treatment, with results supporting this study. PEG-IFN+ribavirin treatment appears to have good long-term results.

In chronic hepatitis C treatment, it is still uncertain whether complete elimination is achieved as a result of the treatment or whether a small number of viruses persist. In former studies using less sensitive tests, 95% of the patients with SVR had undetectable levels of HCV-RNA in the liver within 1 to 2 years after treatment. Only two of the seven patients with HCV-RNA detected in the liver after treatment relapsed after 4 years. In another study, none of the 17 patients with negative HCV-RNA detected in the liver after treatment relapsed at the end of 12 years.^{13,18} On the other hand, only two of the 17 patients with negative HCV-RNA resulting from IFN+ribavirin had negative HCV-RNA in all of their body components including hepatocyte, serum, peripheral blood mononuclear cell, lymphocyte, and macrophage cultures. This suggests that there is a probability of relapse after many years.¹⁹ The clinical significance of low-level HCV-RNA persistence is unknown and further studies must be performed for this issue.

For two of our 196 patients with SVR, HCV-RNA was determined to be positive at a low level at months 18 and 48; however, when both observations were repeated after 3 months they were noted to be negative. The exact reason for transient positivity of HCV-RNA was not clear. It was determined that patients with SVR demonstrated truly durable viral responses and relapsed patients had intermittent and low-grade viraemia.

SVR presumably prevents HCC development.²⁰ None of our patients with SVR demonstrated HCC on long term follow-

up. Improvements in liver fibrosis,²¹ biochemical indicators, fatigue, and life quality²² were detected with SVR. In our batch, no data was available concerning improvements in fibrosis, as there were no adequate end-of-therapy control liver biopsies. When pretreatment ALT levels were compared with ALT on the last control (101.72±78.84 IU/mL [range, 12 to 465 IU/mL] vs 22.52±11.73 IU/mL [range, 8 to 84 IU/mL]), further improvement was observed (p<0.05).

In conclusion, it was found that patients with SVR in chronic hepatitis C demonstrated truly durable responses in the long term follow-up period of 3 years on average and that there was no complication related with liver disease throughout this period.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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