The Efficacy of Short-term Interferon-beta Therapy for Chronic Hepatitis C Patients with Low Virus Load

Yusuke Kawamura¹, Yasuji Arase¹, Kenji Ikeda¹, Fumitaka Suzuki¹, Yoshiyuki Suzuki¹, Masahiro Kobayashi¹, Norio Akuta¹, Tetsuya Hosaka¹, Hitomi Sezaki¹, Hiromi Yatsuji¹, Mariko Kobayashi² and Hiromitsu Kumada¹

Abstract

Objective  The aim of this study was to elucidate the efficacy of short-term interferon (IFN) therapy for chronic hepatitis C patients with low virus load.

Methods  The present study was a retrospective cohort study. Inclusion criteria were biopsy-proven chronic hepatitis, the serum hepatitis C virus (HCV) RNA level of less than 100 KIU/ml, IFN period of 8 weeks or less. One hundred and eleven consecutive patients satisfied above criteria were treated with IFN-beta (dose: 6 MU, daily for 4, 6, or 8 weeks).

Results  Background of clinical profiles were as follows: median (range) age=56 (20-73) years, male/female=64/47, genotype 1b/2a/2b=40/68/3, and median (range) HCV-RNA= 34 (4.5-81) KIU/ml. Out of 111, 64 patients (57.7%) had sustained viral response (SVR). Based on the difference of HCV genotype, the SVR rate was 47.5% (19/40) in genotype 1 and 63.3% (45/71) in genotype 2. In genotype 1, the SVR rate in patients treated with the 8-week regimen was significantly higher than that in patients treated with the 4- or 6-week regimen. In contrast, in genotype 2, the SVR in patients treated with the 8-week regimen was not significantly different from that in patients treated with the 6-week regimen. None of the patients had severe IFN-related side effects.

Conclusions  The 6 or 8-week regimen of IFN-beta therapy is one selection of therapy for chronic hepatitis C patients who have tended to have a SVR and who show IFN-related adverse events.

Key words: chronic hepatitis C, low virus load, interferon, sustained viral response

(Inter Med 47: 355-360, 2008)
(DOI: 10.2169/internalmedicine.47.0454)

Introduction

Current interferon (IFN) therapy for patients with chronic hepatitis C viral infection has been directed at viral clearance. Recent studies reported improvement of therapeutic efficacy when IFN is combined with ribavirin (1-5). Moreover, novel long-acting formulations of IFN known as pegylated IFN induced higher eradication rate of hepatitis C virus (HCV) (6-8). However, IFN is expensive and has a number of serious side effects. Therefore, if the treatment period becomes shorter, it could be preferable.

Several predictive factors of sustained viral response (SVR) to IFN have been identified, and these include a short duration of disease, young age, absence of liver cirrhosis, low HCV-RNA levels, HCV genotype 2a and mutant type of nonstructural 5A region (9-15). Low dose IFN tends to eradicate HCV RNA in patients who had a low serum level of HCV-RNA. However, there is also controversy over how long the IFN therapy should be continued to eradicate HCV RNA in patients. Thus, in this study we evaluated the duration of IFN therapy in order to eradicate HCV RNA in patients who had low serum levels of HCV-RNA.

Abbreviations: HCV: hepatitis C virus, IFN: interferon, SVR: sustained viral response

¹Department of Hepatology, Toranomon Hospital, Tokyo and ²Department of Hepatic Research Unit, Toranomon Hospital, Tokyo
Received for publication July 16, 2007; Accepted for publication November 21, 2007
Correspondence to Dr. Yusuke Kawamura, k-yusuke@toranomon.gr.jp
Materials and Methods

Patients

A total of 111 consecutive chronic hepatitis C patients treated with IFN-beta for HCV RNA clearance at Toranomon Hospital in Tokyo, Japan between 1997 and 2006 were enrolled in this study. This study was a retrospective cohort study. Enrollment criteria were: repeated alanine aminotransferase (ALT) elevation greater than the upper normal limits (ALT normal range: 12-50 IU/L) for more than six months; histological evidence of chronic hepatitis within one year of entry into the trial; positive serum HCVRNA; serum HCV RNA level of less than 100 KIU/ml or 1 Meq/ml; genotype 1b, 2a and 2b. We excluded from the study all of the patients: 1) with concurrent hepatitis B virus (HBV); 2) with a history of IFN therapy; 3) Leukocytes <3,000/mm³, platelets <80,000/mm³ and bilirubin >1.5 mg/ml before IFN therapy.

One hundred eleven patients received IFN at a dose of 6 million units (MU) of natural IFN-beta (Toray Industries or Daiichi Pharmaceutical Co., Tokyo, Japan) daily for 4, 6 or 8 weeks. In general, patients were treated with IFN for 8 weeks. Eleven patients treated for 4 weeks and thirty patients treated for 6 weeks were assigned by randomized controlled trial. We regarded sustained viral response (SVR) to therapy as clearance of HCV RNA by RT-nested PCR (16) or amplicor method (17) for more than 6 months after cessation of therapy. Our study was approved by the institutional ethics review board of our hospital. The physician in charge explained the purpose and method of this clinical trial as well as the potential adverse reactions to each patient, who later gave his/her informed consent for participation.

Blood testing

Blood samples were obtained just before IFN therapy and stored at -80°C. Using these blood samples, HCV-RNA levels before IFN therapy were analyzed by quantitative PCR assay (Amplipcr GT-HCV Monitor Version 2.0, Roche Molecular Systems) (18).

On the other hand, serum HCV-RNA at 6 months after the termination of IFN therapy was analyzed by the qualitative PCR assay or RT-nested PCR. The lower detection limit of the qualitative assay is 100 copies/ ml. HCV genotype was examined by the PCR assay, using a mixture of primers for the six subtypes known to exist in Japan, as reported previously (19).

Liver histology

Liver biopsy specimens were obtained percutaneously or by peritoneoscopy using a modified Vim Silverman needle.

Table 1. Clinical Characteristics before Interferon Therapy in Chronic Hepatitis C Patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>(n=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years old) †</td>
<td>56(20-73)</td>
</tr>
<tr>
<td>Male/female †</td>
<td>64/47</td>
</tr>
<tr>
<td>Liver histology (fibrosis, 1/2/3) †</td>
<td>60/25/26</td>
</tr>
<tr>
<td>HCV genotype(1b/2a/2b) †</td>
<td>40/68/3</td>
</tr>
<tr>
<td>HCV load (KIU/ml) †</td>
<td>34 (4.5-81)</td>
</tr>
<tr>
<td>AST (IU/L) †</td>
<td>56 (14-226)</td>
</tr>
<tr>
<td>ALT (IU/L) †</td>
<td>76 (15-434)</td>
</tr>
</tbody>
</table>

*ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; and HCV, hepatitis C virus.
† Data are expressed as median(range).
‡ Data are number of patients.
Table 2. Predictive Factors for SVR in Patients with HCV Genotype 1*

<table>
<thead>
<tr>
<th>Factor</th>
<th>Category</th>
<th>Odds ratio</th>
<th>95% CI†</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Period of IFN therapy (week)</td>
<td>4 or 6/8</td>
<td>1/8.93</td>
<td>2.14-37.03</td>
<td>0.003</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>&lt;76≥76</td>
<td>1/2.17</td>
<td>0.85-5.55</td>
<td>0.102</td>
</tr>
<tr>
<td>Sex</td>
<td>Man / Woman</td>
<td>1/0.56</td>
<td>0.16-2.00</td>
<td>0.367</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>&lt;100≥100</td>
<td>1/1.67</td>
<td>0.47-5.93</td>
<td>0.430</td>
</tr>
<tr>
<td>Liver histology (fibrosis)</td>
<td>1 /2,3,4</td>
<td>1/0.79</td>
<td>0.39-1.60</td>
<td>0.507</td>
</tr>
<tr>
<td>Age (years)</td>
<td>&lt;50/≥50</td>
<td>1/0.80</td>
<td>0.23-2.79</td>
<td>0.726</td>
</tr>
</tbody>
</table>

*ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; HCV, hepatitis C virus; IFN, interferon and CI; confidence interval.

Results

Patients' characteristics

Table 1 shows the characteristics of the 111 patients who received IFN therapy. A total of 40 patients showed HCV genotype 1 and the remaining 71 patients showed HCV genotype 2.

Efficacy of treatment

Out of 111, 64 patients (57.7%) had SVR. Based on the difference of HCV genotype, the SVR rate was 47.5% (19/40) in genotype 1 and 63.3% (45/71) in genotype 2. We then investigated the factors associated with SVR after termination of IFN. Univariate analysis in patients with genotype 1 identified the following one factor that influenced SVR when the period of IFN treatment was 8 weeks (Table 2). As one factor was associated with SVR, we did not evaluate the multivariate analysis.

On the other hand, univariate analysis in patients with genotype 2 did not identify the factor that influenced SVR (Table 3). In genotype 2, the SVR in patients treated with...
Table 3. Predictive Factors for SVR in Patients with HCV Genotype 2 *

<table>
<thead>
<tr>
<th>Factor</th>
<th>Category</th>
<th>Odds ratio</th>
<th>95% CI†</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST (IU/L)</td>
<td>&lt;76 /≥76</td>
<td>1/2.21</td>
<td>0.80-6.14</td>
<td>0.126</td>
</tr>
<tr>
<td>Sex</td>
<td>Man / Woman</td>
<td>1/0.61</td>
<td>0.22-1.64</td>
<td>0.324</td>
</tr>
<tr>
<td>Period of IFN</td>
<td>4 or 6/ 8</td>
<td>1/1.63</td>
<td>0.57-4.69</td>
<td>0.361</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>&lt;100/≥100</td>
<td>1/1.22</td>
<td>0.41-3.57</td>
<td>0.721</td>
</tr>
<tr>
<td>Age (years)</td>
<td>&lt;50/ ≥50</td>
<td>1/0.80</td>
<td>0.23-2.79</td>
<td>0.726</td>
</tr>
<tr>
<td>Liver histology</td>
<td>1/2,3</td>
<td>1/0.88</td>
<td>0.54-1.70</td>
<td>0.876</td>
</tr>
</tbody>
</table>

*ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; HCV, hepatitis C virus; and IFN, interferon and CI; confidence interval.

Table 4. SVR Based on HCV Genotype and Administration Period of Interferon

<table>
<thead>
<tr>
<th>HCV genotype</th>
<th>Administration period (week)</th>
<th>4W (%)</th>
<th>6W (%)</th>
<th>8W (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1 †</td>
<td>0% (0/6)</td>
<td>33.3% (5/15)</td>
<td>73.7% (14/19)</td>
<td></td>
</tr>
<tr>
<td>Genotype 2 ‡</td>
<td>40% (2/5)</td>
<td>60% (9/15)</td>
<td>66.7% (34/51)</td>
<td></td>
</tr>
</tbody>
</table>

*HCV indicates hepatitis C virus; and SVR, sustained virological response.
† p <0.001 in genotype 1, p =0.32 in genotype 2 by Cochran-Armitage method
‡ Three patients had HCV genotype 2b. These three patients were treated for 8 weeks and all the patients showed SVR. Remaining patients had genotype 2a.

the 8-week regimen was similar statistically to that in patients treated with the 4- or 6-week regimen.

Table 4 shows the SVR based on the HCV genotype and period of IFN therapy. According to Cochran-Armitage method, the 8-week IFN therapy regimen was the best in order to eradicate HCV RNA in genotype 1. On the other hand, in genotype 2, the 6-week regimen was almost the same as the 8-week regimen.

Adverse events

Within one week after the initiation of treatment, flu-like symptoms appeared in all the patients. Pain in the joints or muscle occurred in 50 cases. However, none of the patients withdrew from this treatment due to IFN-related side effects.
We have described the efficacy of short-term IFN-beta therapy for chronic hepatitis C patients with low virus load. The present study was limited by a retrospective cohort trial. However, several findings from the present study have direct implications for the short-term IFN treatment of CH patients with low virus load. First, HCV RNA was cleared in more than 50% patients. Second, no patients withdrew from the treatment due to IFN-related side effects. Okanoue et al reported that side effects occurred when the daily IFN dose was increased (21). However, in the 8-week study period, there were no serious side effects. Third, the 8-week regimen of IFN therapy was preferable to eradicate HCV RNA compared to the 4 or 6-week regimen in genotype 1. On the other hand, in genotype 2, SVR by the 6-week regimen of IFN therapy was not significantly different from SVR by the 8-week regimen. These results indicate that 1) in patients with genotype 1 and low virus load, the 8-week regimen of IFN was recommended as the first treatment, 2) in patients with genotype 2 and low virus load, the 6-week regimen of IFN was recommended as the first treatment. This result is likely in agreement with several previous clinical trials (22-26).

In patients with genotype 1b and a high load of HCV RNA, the clearance rate of HCV-RNA is less than 10% by the usual 6-month course of IFN monotherapy. In these IFN-resistant patients, the eradication rate of HCV-RNA was 50.9% (220/432) in genotype 1b, 79.9% (279/349) in genotype 2a, and 71.4% (45/63) in genotype 2b. These results indicate that SVR of the 24-week regimen was higher than that of the short term regimen in genotype 2. However, prolonged IFN therapy is often associated with various side effects. A lower total dose and shorter administration period of IFN would be preferable in terms of both cost and safety.

Fortunately, patients with low HCV-RNA levels tend to eradicate HCV RNA with a low dose of IFN. The present study indicates that short-term IFN-beta therapy has no severe side effects. Thus, short-term IFN therapy is recommended for the patients who tend to have a SVR and have IFN-induced adverse events.

For the present, combined IFN and ribavirin therapy is the standard therapy for chronic hepatitis C patients with genotype 1b and a high load of HCV-RNA. Next, in our hospital SVR of the 24-week IFN regimen in patients with a low load of HCV-RNA was 50.9% (220/432) in genotype 1b, 79.9% (279/349) in genotype 2a, and 71.4% (45/63) in genotype 2b. These results indicate that SVR of the 24-week regimen was higher than that of the short term regimen in genotype 2. However, prolonged IFN therapy is often associated with various side effects. A lower total dose and shorter administration period of IFN would be preferable in terms of both cost and safety.

Fortunately, patients with low HCV-RNA levels tend to eradicate HCV RNA with a low dose of IFN. The present study indicates that short-term IFN-beta therapy has no severe side effects. Thus, short-term IFN therapy is recommended for the patients who tend to have a SVR and have IFN-induced adverse events.

Acknowledgement
The present work was supported in part by grants-in-aid from Okinawa Memorial Institute for Medical Research and Japanese Ministry of Health, Labour and Welfare.

References


