Efficacy of Interferon Monotherapy for Chronic Hepatitis C: Investigation of appropriate treatment with respect to histologic and virologic factors, and usefulness of twice-daily interferon-\( \beta \) administration as induction therapy

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Abstract

In order to determine the most appropriate interferon (IFN) therapy according to patient background and to evaluate the efficacy of twice-daily IFN-\( \beta \) induction therapy (\( \beta \) 2 therapy), 320 patients with chronic hepatitis C who underwent various IFN monotherapy regimens were retrospectively analyzed. Sustained virological response (SVR) and biochemical response (BR) rates were calculated with respect to HCV serogroup (SG), pretreatment viral load, histological stage, total IFN dose, and IFN regimen (Low, Medium, High, and \( \beta \) 2 therapy). The total IFN dose in \( \beta \) 2 therapy was almost equal to that in the High group. The SVR rate for \( \beta \) 2 therapy in patients with stage F0-2 was as follows: SG 1 infection and high viral load 27\%, SG 1 infection and low viral load 80\%, and SG 2 infection and high viral load 78\%, and was higher than that for the other regimens. The combined efficacy rate, including BR, for \( \beta \) 2 therapy was the highest among all regimens, indicating that this should be the first choice of treatment for the above types of patients. The SVR rate for \( \beta \) 2 therapy in patients with SG2 infection and low viral load was 90\%, and was 70\% even in the Low group (total dose: about 300 MU), and thus the initial therapy for these patients could be short-term. Among patients with stage F3/4 the overall SVR rate for patients with low viral load was 41\% (11/27), which suggests that IFN therapy should be actively considered.

Key Words:
hepatitis C, interferon monotherapy, interferon-\( \beta \), induction therapy, twice-daily administration

Introduction

Interferon (IFN) has been used for the treatment of chronic hepatitis C in Japan for the past eleven years, and during this time, it has become to be known that in some patients, IFN completely eradicates hepatitis C virus (HCV), improves hepatic fibrosis, and reduces the risk for hepatocellular carcinoma\(^{1,2}\). IFN is now the first choice of therapy for the treatment of chronic hepatitis C. Because HCV eradication was achieved in only a small number of patients initially, various therapeutic regimens have been introduced to improve its efficacy. Of these, the twice-daily
IFN-α administration regimen has been reported to have potent antiviral effects\(^3\)\(^-\)\(^5\), and has been most widely used as an induction therapy in our department since 1996. Until three years ago, IFN therapy could only be performed once in treating chronic hepatitis C and only for up to six months in Japan. As a result, when it was indicated, physicians were forced to select the most effective therapy available at the time. On the other hand, when IFN therapy was originally applied to the treatment of this disease, due to a lack of clinical usage and fear of adverse reactions, low-dose and/or short duration of administration was most often performed, and there were various changes in IFN dose, administration period and regimen during this time.

In recent years, combination therapy of IFN and ribavirin has been approved in Japan, and restrictions regarding duration and frequency of IFN therapy have been eliminated. Consequently, it is now possible to tailor a therapeutic regimen to each individual patient. The efficacy of IFN therapy for hepatitis C is known to vary greatly depending on both viral and host factors, and IFN can now be administered while taking these factors into account. Ribavirin has already been used to treat patients with chronic hepatitis C in Europe and America, with basic guidelines for ribavirin-IFN combination therapy being established in 1998\(^6\), followed by similar guidelines being established in the Asia-Pacific region\(^7\). However, these guidelines cannot be adopted in Japan because ribavirin can be administered for up to six months only to patients with high viral loads or retreating patients.

In the present study, we investigated the outcomes of IFN monotherapy performed in our department over the past ten years with respect to various factors by evaluating the clinical significance of twice-daily IFN-α administration as induction therapy, and determining which IFN therapy is best suited to the various patient background factors.

**Patients and Methods**

Between January 1992 and December 2001, IFN was administered at our department for the treatment of chronic hepatitis C to a total of 357 patients. While excluding one patient co-infected with human immunodeficiency virus, one patient with autoimmune hepatitis, thirteen patients who had discontinued the treatment because of side effects (8 patients with severe dullness, 2 with depression, 1 with pyrexia, 1 with cerebral infarction, 1 with nephrotic syndrome) with a total dose of less than 252 MU, four patients who received special agents (collagen-combined IFN), two patients who consumed more than 80 g of alcohol daily for more than five years, and two patients who failed to visit the hospital after completion of therapy, 334 patients served as subjects. All patients were negative for serum hepatitis B surface antigen. The following types of IFN were used: IFN-α 2a, IFN-α 2b, natural IFN-α (HLBI, Ball-1), and natural IFN-β. The patients were divided into the following four groups with respect to total IFN dose and regimen:

- **Group A**: Low IFN dose (252-336 MU, daily administration of 6 MU of IFN-α for 6 or 8 weeks, or daily administration of 6 MU of IFN-β for 2 weeks followed by three times weekly administration for 10 to 14 weeks, primarily treated from 1992 to 1994).
- **Group B**: Medium IFN dose (372-558 MU, daily administration of 6 MU of IFN-α for 6 or 8 weeks, or daily administration of 9-10 MU of IFN-β for 2 weeks followed by three times weekly administration for 16 to 24 weeks, or daily administration of 9-10 MU of IFN-α for 2 weeks followed by three times weekly administration of 5-6 MU for 22-24 weeks, primarily treated in 1993 and 1994).
- **Group C**: High IFN dose (612-940 MU, daily administration of 9 MU of IFN-α for 4 weeks followed by three times weekly administration of 6 MU for 20 weeks, or daily administration of 9-10 MU of IFN-β for 2 weeks followed by three times weekly administration of 9-10 MU for 20-22 weeks, primarily treated from 1993 to 1995).
- **Group D**: IFN-β (252-908 MU, 3 MU of IFN-β was initially administered twice-daily for 2-4 weeks in one of the above regimens, treated from 1996 to 2001).

HCV RNA genotype was determined by serogrouping of serum antibodies with an assumption that genotypes 1a and 1b correspond to serogroup 1 (SG 1), while genotypes 2a and 2b correspond to serogroup 2 (SG 2)\(^8\). The level of HCV RNA was quantified by competitive reverse-transcription polymerase chain reaction (CRT-PCR) assay (Mitsubishi BCL, Tokyo, Japan), branched-
DNA probe assay (bDNA probe assay, Chiron Dai-ichi Kagaku, Tokyo, Japan) or commercial RT-PCR assay (Amplicor Monitor ver. 2, Nippon Roche, Tokyo, Japan). In all SG 2 patients, it was quantified by CRT-PCR or Amplicor Monitor (ver. 2) because of their equal sensitivity for all genotypes. According to correlation among HCV-RNA titers measured with CRT-PCR, bDNA assay and Amplicor Monitor ver. 2 in several patients (Table 1), high viral load was defined as follows: CRT-PCR ≥ 10^6 IU/L, bDNA probe assay ≥ 1 Meq/mL, and Amplicor Monitor ≥ 100 KIU/ml. Hepatic fibrosis was assessed by pretreatment biopsy specimen according to the New Inuyama classification. In other words, depending on the severity of fibrosis, patients were divided into two groups: absence of or moderate fibrosis (F0, F1, and F2) and advanced fibrosis (F3 and F4).

Assessment of therapeutic efficacy: Sustained virological response (SVR) was defined as negative serum HCV RNA, as assessed by the standardized qualitative HCV RNA assay (Amplicor HCV ver. 2, Nippon Roche, Tokyo, Japan), for more than six months after the end of IFN therapy, while biochemical response (BR) was defined as positive serum HCV RNA but normal ALT for more than one year after the end of IFN therapy. Other responses were classified as non-responses (NR).

Statistical analysis: A Fisher’s exact probability test was used to compare data between the two groups, while a Fisher’s PLSD was used to compare data among three or more groups.

**Results**

Table 2 shows the patient profiles in each treatment group. While there were no marked differences in male-female ratio, age, HCV serogroup and HCV RNA load, the ratio of patients with advanced fibrosis for Group D was lower than that for group A, B, C (p=0.0121, 0.0007, and 0.0833, respectively).

Relationship between SVR rate and various factors

1. **SVR rate and HCV serogroup**

   Among patients with SG1 infection, the SVR rate was 8-36% for the four groups. However, among patients with SG2 infection, the SVR rate was significantly higher at 52-78% for all groups (A: p=0.0022, B: p=0.0159, C: p<0.0001, and D: p=0.0002) (Figure 1).

2. **SVR rate and HCV RNA load**

   Among patients with high pretreatment viral load, SVR rate was 4-46% for the four groups. However, among patients with low pretreatment viral load, the SVR rate was significantly higher at 39-78% for all groups (A: p=0.0001, B: p=0.0005, C: p<0.0001, and D: p=0.0090).
Figure 1. Sustained virological response (SVR) according to HCV serological group (Fig.1-1), pretreatment viral load (Fig.1-2), and histological stage (Fig.1-3). A, low dose of total interferon; B, medium dose; C, high dose; D, twice-daily IFN \( \Delta \) administration as initial treatment.

\( \square p<0.01, \quad \Box p<0.05 \)

Figure 2. Sustained virological response (SVR) and biochemical response (BR) rates according to HCV serological group, pretreatment viral load, and total interferon dose/regimen in patients with histological stage F0-2. A, low dose of total interferon; B, medium dose; C, high dose; D, twice-daily IFN \( \Delta \) administration as initial treatment. Statistical analyses were performed using Fisher's PLSD.

\( \square 1 \ p<0.01 : \text{SVR+BR}, \ \text{SVR} \quad \square 2 \ p<0.01 : \text{SVR+BR}, \ p<0.05 : \text{SVR} \)

\( \square 3 \ p<0.05 : \text{SVR+BR}, \ p<0.01 : \text{SVR} \quad \square 4 \ p<0.05 : \text{SVR+BR}, \ \text{SVR} \)
3. SVR rate and histological stage

The SVR rate for patients with stage F0-2 tended to be higher than that for the patients with stage F3/4, but there was a significant difference between them only in Group D \((p=0.0392)\).

Total IFN doses and regimens with respect to matching HCV serogroup, HCV RNA load and histological stage

This analysis was conducted in 320 patients excluding those with mixed genotypes or unknown viral loads.

1. Stage F0-2, SG1 infection, and high viral load

The SVR rate for patients with stage F0-2, SG1 infection and high viral load was generally low. The SVR rate for Group D (27%, 8/30) was significantly higher than that for Group A (3%, 1/31, \(p=0.0062\)) or Group C (6%, 1/18, \(p=0.0328\)) (Figure 2). In addition, the combined efficacy rate, including BR, for Groups A, B, C, and D was 6, 27, 11, and 37%, respectively. There was a significant difference between Groups D and A and between Groups D and C \((p=0.0023\) and \(p=0.0328\), respectively). Among the 13 SVR cases, the maximum HCV RNA load as assessed by CRT-PCR, bDNA probe assay and Amplicor monitor was \(10^6\) copy/mL, 4.3 Meq/mL and 380 KIU/mL, respectively. Among the three BR cases of Group D, the viral load did not exceed 700 KIU/mL.

2. Stage F0-2, SG1 infection and low viral load

While the SVR rate for Group D was high at 80%, that for Groups A, B, and C was significantly lower at 21, 36, and 38% \((p=0.0034, 0.0161\) and 0.0148, respectively). The combined efficacy rate for Group D (90%) was significantly higher than that for Groups A, B, and C \((p=0.0036, p=0.0062\) and \(p=0.0066\), respectively).
3. Stage F0-2, SG2 infection and high viral load

The SVR rate for Group D was favorable at 78%, but that for Groups A and B was significantly lower at 11 and 33% ($p=0.0062$ and $p=0.0066$, respectively). The BR rate for Group A was 56%, and there was a significant difference in the combined efficacy rate between Groups D and A ($p=0.0114$) and between Groups D and B ($p=0.0398$).

4. Stage F0-2, SG2 infection and low viral load

The SVR rate for all four groups was high, and while that for Group A was the lowest, it was still favorable at 69%. The SVR rate for Groups C and D was above 90%, and there were no significant differences among the four groups. There was only a single case of BR in Group B, and there were no significant differences in the total efficacy rate among the four groups.

5. Stage F3/4

Because the number of patients with advanced fibrosis (F3 or F4) was low for all four groups, no intergroup comparison was conducted (Figure 3). While the SVR rate for the patients with SG1 infection and high viral load was extremely low at 3% (1/39), that for SG1 infection and low viral load was 42% (5/12), SG2 infection and high viral load 25% (2/8), and SG2 infection and low viral load 40% (6/15).

Mixed genotype

Ten patients had chronic hepatitis C of mixed genotypes: Seven patients had genotypes 1b and 2b and three patients had genotypes 1b and 2a (Table 3). Although RNA load, histological stage and therapy regimen varied among these patients, there were six SVR cases and one BR case, and the total efficacy rate for these patients was favorable at 70%.

**Discussion**

The efficacy of IFN therapy for chronic hepatitis C was initially assessed in terms of sustained ALT normalization after the end of therapy \(^{11}\), but after the HCV is shown to be completely eradicated, virological response also tends to be used to assess the efficacy of IFN therapy \(^{12}\). Furthermore, even when the virus is not eradicated, when ALT is sustained at normal levels for a long period of time after therapy, the risk for hepatocellular carcinoma is reduced, as is the case with SVR \(^{1}\). This sustained response is referred to as the biochemical response to IFN therapy. With regard to BR, some reports \(^{13}\) suggested that it is associated with patients having mild fibrosis and high viral load, while Nishiguchi et al. \(^{15}\) suggested a correlation between BR and viral mutation. However, the causes, including background factors, of BR remain to be elucidated. With regard to SVR, host factors, such as gender, age, infection period and alcohol consumption; viral factors, such as HCV genotype, and viral mutation; and therapeutic factors, such as IFN dose, have been documented. However, the results of recent multivariate analyses and meta-analysis have shown that the independent factors associated with SVR are HCV genotype, HCV RNA load, hepatic fibrosis, and total IFN dose \(^{16-18}\). In the present study, we analyzed these four factors in a total of 320 patients.

With regard to the relationship between serogroup and SVR, the SVR rate was high for patients with SG2 infection in all four groups, and as to the relationship between viral load and SVR, the SVR rate was high for the patients with low viral loads, which agreed with the results of past studies. The SVR rate also tended to be higher for patients with stage F0-2, but a significant difference in SVR rate between stage F3/4 and F0-2 was seen in only one group. However, since there were few stage F3/4 patients in the present study, the relationship between

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**Table 3. Profile and IFN Effect of the Patients with Mixed HCV Genotypes**

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (y)</th>
<th>Gender</th>
<th>Serogroup</th>
<th>RNA load</th>
<th>Histological stage</th>
<th>Treatment</th>
<th>IFN dose (IU)</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>51 M</td>
<td>1b+2a</td>
<td>4</td>
<td>F4</td>
<td>B</td>
<td>SVR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>51 M</td>
<td>1b+2a</td>
<td>5</td>
<td>F3</td>
<td>A</td>
<td>SVR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>61 F</td>
<td>1b+2a</td>
<td>3-4</td>
<td>F3</td>
<td>A</td>
<td>SVR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>34 F</td>
<td>1b+2b</td>
<td>3-4</td>
<td>F1</td>
<td>A</td>
<td>SVR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>38 M</td>
<td>1b+2b</td>
<td>3</td>
<td>F1</td>
<td>F1</td>
<td>no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>46 M</td>
<td>1b+2b</td>
<td>5-6</td>
<td>F3</td>
<td>C</td>
<td>BR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>45 F</td>
<td>1b+2b</td>
<td>6-7</td>
<td>F2</td>
<td>C</td>
<td>SVR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>50 M</td>
<td>1b+2b</td>
<td>3</td>
<td>F1</td>
<td>D</td>
<td>SVR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>53 M</td>
<td>1b+2b</td>
<td>7</td>
<td>F2</td>
<td>C</td>
<td>no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>53 M</td>
<td>1b+2b</td>
<td>4</td>
<td>F1</td>
<td>B</td>
<td>no</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*[^3]{CRF-PCR: log 10 copies/mL}[^2]*

[^1]: Sato A Suzuki H et al.
hepatic fibrosis and SVR could not be sufficiently assessed. Concerning the relation of hepatic fibrosis to IFN response many studies have suggested that advanced liver fibrosis decreases response to IFN treatment \(^{19-21}\), and multivariate analysis showed the histological stage was one of the predictive factors of the treatment \(^{16}\). But HCV genotype and pretreatment viral load were shown to be more important factors for long term response to IFN treatment \(^{22}\), and which indicates viral factors must be weighed rather than histological stage when IFN therapy is considered. In the investigation of total IFN dose and regimen with matching background factors, because the number of patients with stage F3/4 was low, the four regimens were not compared. However, of the 39 patients with stage F3/4, SG1 infection and high viral load, SVR was achieved in only one patient, thus suggesting that other treatments, such as ribavirin-combined therapy which achieved equivalent SVR rates in patients with advanced histological stage to those in patients with mild fibrosis \(^{23,24}\), should be considered. Furthermore, besides SVR, it is necessary to investigate therapy to control hepatic fibrosis and to reduce the risk for hepatocellular carcinoma. Of the 27 patients with advanced fibrosis and low viral load, SVR was achieved in 11 patients. Thus, IFN therapy should be initiated but more studies are needed to identify the most appropriate regimen for these patients.

In the patients with stage F0-2, interesting findings were obtained. First of all, there was some correlation between total IFN dose and efficacy, and twice-daily IFN-\(\alpha\) induction therapy (Group D) was the most effective, except for those with SG2 infection and low viral load. Secondly, among the patients with SG2 infection and low viral load, there were no marked differences in SVR rate with respect to total IFN doses or regimens.

Chronic hepatitis C patients with SG1 infection and high viral load have been known to be IFN-resistant, and the SVR rate for standard IFN therapy in Japan (total dose: 480-528 MU) has been reported at less than 10\%. Recently, Arase, et al. \(^{25}\) reported that 48 weeks of IFN therapy (total dose: 1058 MU) achieved a SVR rate of 17.4\%, and Ino, et al. \(^{26}\) reported an SVR rate of 25\% with 48 weeks of therapy. In the present study, the SVR rate for twice-daily IFN-\(\alpha\) induction therapy for a total of 24 weeks was comparable to the above results, and when including BR, the combined efficacy rate was 36.7\%, with viral load being less than 5.0 Meq/mL or 700 KIU/mL in every patient. Therefore, in patients with a viral load within this range, the risk of adverse reactions associated with ribavirin (e.g., hemolytic anemia or teratogenicity) must be weighed, but when the viral load is higher, ribavirin combination therapy or long-term monotherapy should be considered. Among patients with SG1 infection and low viral load, the usefulness of twice-daily IFN-\(\alpha\) induction therapy (Group D) was the highest, thus suggesting that this therapy should be the first choice. In addition, among patients with SG2 infection and high viral load, the SVR rate for Group D was about 80\%, and as a result, twice-daily IFN-\(\alpha\) induction therapy should be the first choice in treating these patients. However, further studies are necessary because there were a small number of patients with SG2 infection and high viral load in Groups A, B and C. Though the mechanism of potent anti viral effect of twice-daily IFN-\(\alpha\) administration is unknown, our data suggest twice-daily IFN-\(\alpha\) induction therapy is useful for some patients with chronic hepatitis C. In the course of twice-daily IFN-\(\alpha\) administration marked decrease of platelet count and proteinuria are frequent and sometime severe, so the assessment for indication of therapy and monitoring in the course of treatment are needed. On the other hand, among patients with SG2 infection and low viral load, the SVR rate for regimens with approximately 300 MU of IFN was about 70\%. Shiratori et al. \(^{27}\) reported that 12 weeks daily-IFN treatment (median total dose 432 MU) could achieved 16/18 SVR in patients with SG2 infection and low viral load, and thus initial therapy for these patients could be short-term, lasting 8 to 12 weeks. Furthermore, in these patients, therapeutic efficacy would be further improved by thoroughly investigating pretreatment viral load, as well as viral kinetics during the early phases of treatment, and comparing genotype 2a and 2b patients.
Conclusions

In chronic hepatitis C, favorable results can be expected with six-month IFN monotherapy in which twice-daily IFN-\(\alpha\) is administered as an induction therapy, except when patients have SG1 infection and high viral load. Furthermore, 70% of patients with SG2 infection and low viral load can be expected to achieve SVR even when conventional IFN therapy with low total dose is administered. On the other hand, in patients with SG1 infection and very high viral load, ribavirin-combined therapy or long-term IFN monotherapy should be selected. As to patients with advanced fibrosis, IFN administration should be considered since SVR could be achieved when viral load is low, but further investigation is needed in order to establish more appropriate regimens.

References


C 型慢性肝炎におけるインターフェロン単独療法の効果：
ウイルス学的、組織学的因子に対応した治療法の検討および
IFN・1 日 2 回導入療法の有用性について

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抄 録

1992 年 1 月から 2001 年 12 月の 10 年間に聖マリアンナ医科大学横浜市西部病院で IFN 単独療法を行った C 型慢性肝炎 320 例について症例背景および IFN 治療法別にその有効性を検討した。各症例を肝線維化進展度、HCV セログループ（SG）、HCV-RNA 量により分類し、また IFN 総投与量/治療法別に低用量、中用量、高用量および IFN・1 日 2 回導入療法（○2 回）に分け、それぞれのウイルス駆除（SVR）率および ALT 持続正常化（BR）率を解析した。○2 回の平均総投与量は高用量と同等であったが、SVR 率は線維化度（F0-2）例で SG1・高ウイルス量群、SG1・低ウイルス量群、SG2・高ウイルス量群においては他の治療法に比べ高かった（それぞれ 27%，80%，78%）。BR を含む統合有効率でも ○2 回は各群で最も高く、これらの群における第一選択の治療法と考えられた。しかし SG1・超高ウイルス量（700 KIU/ml 以上）での有効例はなく、この群ではリパビリン併用療法または単独長期投与が考慮されるべきであると考えた。SG2・低ウイルス量群においても ○2 回は 90% の SVR 率を示したが、低用量（約 300 MU）でも 70% に SVR が得られ、この群の初回治療は短期間の治療を試みてもよいと思われる。線維化度（F3, 4）例では低ウイルス量例において全体で 41%（11/27）の SVR を認め、この群には積極的に IFN 療法を行うべきであると考えた。