Duration of Chronic HCV Infection and Efficacy of Interferon in Chronic Hepatitis C Patients with a History of Blood Transfusion

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Abstract

To investigate correlations between the interval between blood transfusion and the start of IFN therapy, and IFN efficacy, we studied chronic hepatitis C patients with a history of blood transfusion. The subjects were 122 patients with chronic hepatitis C and a history of blood transfusion at 64 institutions. The patients were treated with high or low-dose IFN. High-dose therapy consisted of intramuscular injection of human lymphoblastoid interferon (HLBI), 6 × 10⁶ IU daily for 2 weeks, then 3 times a week for 22 weeks, and low-dose interferon therapy of intramuscular injection of HLBI, 6 × 10⁶ IU daily for 2 weeks, then 3 × 10⁶ IU 3 times a week for 22 weeks. Normal serum ALT levels for 6 months or more after completing IFN (complete response) were found in 44/122 (36.2%) patients and HCV RNA was no longer detectable after completing IFN therapy in 19/68 (27.9%). Patients in whom the interval between blood transfusion and the start of IFN therapy was less than 20 years had significantly higher rates of HCV RNA-negative complete response than those in whom the interval was 20 years or more (p<0.039).

When chronic HCV infection is caused by blood transfusion, the efficacy of IFN depends on the duration of chronic HCV infection. Since the duration of HCV infection is a factor in predicting efficacy, early IFN therapy may be more effective.

Introduction

Many chronic hepatitis C patients are treated with IFN1)~3). Factors that influence IFN efficacy in these patients include serum HCV RNA level, HCV genotype, and stage of liver disease4)~12). In addition, resistance to IFN therapy is reported to be regulated by the NS5A region of the HCV RNA gene13). These findings prompted us to evaluate IFN efficacy in association with the duration of HCV infection.

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infection. Several factors are involved in long periods of chronic HCV infection. As viral factors, both quantity of HCV RNA and resistance of HCV to IFN vary with time, and immune responses and stage of liver disease are important as host factors. In this study, we evaluated IFN efficacy in relation to the interval between blood transfusion and the start of IFN therapy, and also studied the association with histological progression in the liver.

**Subjects and Methods**

*Subjects*

The subjects were chronic hepatitis C patients with an accurate documented history of blood transfusion. The following patients were excluded from the study: those infected with HCV via transmission routes other than blood transfusion; those with autoimmune hepatitis or alcohol-induced liver injury; those given IFN or prednisolone within 3 months of the study; and those with a history of glycyrrhizin administration within one month of the study. After receiving an explanation of the objectives, methods, possible results, and side effects, all of the patients gave their informed consent to participate in the study. The diagnosis of chronic hepatitis was based on liver biopsy specimens obtained within a year of the study. The diagnosis of hepatitis C was made by assaying anti-HCV and/or HCV RNA. All subjects were negative for HBs antigen.

*IFN therapy*

Human lymphoblastoid interferon (HLBI; Sumitomo Pharmaceutical Co., Ltd. Tokyo, Japan) was used to treat all patients. The physician in charge determined whether a patient received a low- or high-dose regimen. The low-dose regimen consisted of intramuscular HLBI, 6 x 10⁶ IU daily for 2 weeks followed by 3 x 10⁶ IU 3 times a week for 22 weeks, total dose, 270 x 10⁶ IU and the high-dose regimen, of intramuscular HLBI, 6 x 10⁶ IU daily for 2 weeks followed by 6 x 10⁶ IU 3 times a week, total dose, 480 x 10⁶ IU.

*Liver histopathology before IFN therapy*

Liver biopsy specimens were obtained from 143 patients with a past history of blood transfusion. The specimens were stained with hematoxylin and eosin and with Azan Mallory stain. Each biopsy specimen was blindly evaluated independently by 3 liver pathologist (M.K., O.I., and S.S) based on a staging and grading scoring system recommended by Sheuer et al. Each provided a numerical score for the grade of portal/periportal necroinflammation (0-4), grade of lobular inflammation (0-4), their sum (final grade), and score for the stage of hepatic fibrosis (0-4). When the pathologists interpretations of liver biopsy specimens differed, the scores were arrived at in conference. None of the scores differed by more than one point. We also examined the relationship between IFN efficacy and the histopathological findings in regard to inflammatory cell infiltration in the portal tract, piecemeal necrosis, lymphoid follicles and/or aggregate in the portal tract, and fatty change.

*Evaluation of IFN efficacy*

Evaluation of IFN efficacy was based on serum ALT levels and HCV RNA measurements. Serum ALT criteria were: “complete response”, serum ALT level returned to normal within 6 months after completing IFN therapy and remained normal for another 6 months or more; “partial response”, serum ALT level was less than twice the upper limit of normal and maintained at that level for another 6 months or more; “no change”, results other than the above.

Serum HCV RNA measurements were only performed in patients whose HCV RNA could be measured immediately before starting, at the completion, and 6 months after the completion of IFN therapy. The criteria were as follows: a) “HCV RNA-negative complete response”, those patients judged to have a complete response based on their serum ALT levels who were HCV RNA-negative 6 moths after completing IFN therapy; b) “HCV RNA-positive complete response”, patients HCV
RNA-positive 6 months after completion of IFN therapy; c) “HCV RNA-positive partial response”, those judged to have a partial response based on their serum ALT levels who remained HCV RNA-positive; d) “no change”, those judged “no change” based on their serum ALT levels who remained HCV RNA-positive. HCV RNA was measured by RT-PCR with a 5’ noncoding region primer.

**Statistical analysis**

Fisher’s exact test, Wilcoxon’s rank sum test, Spearman’s rank correlation, and Student’s t-test were used for statistical analyses. Differences were considered significant when P < 0.05.

**Results**

A total of 176 patients were registered for the study, but 54 were excluded for the following reasons: 15 because blood transfusion could not be documented or had been received within 12 months and 39 because they did not complete the course of IFN due to adverse effects or being lost to follow-up. Thus, 122 patients (21 low-dose and 101 high-dose) were included in the study.

Table 1 shows the characteristics of the 122 patients. Although there were more patients in the high-dose group than in the low-dose group, there were no significant differences between the groups in regard to sex, mean age, interval between from blood transfusion and the start of IFN therapy, or serum ALT or albumin levels.

**IFN efficacy based on serum ALT response (Table 2)**

Based on serum ALT levels, 43/122 (35.2%) had complete responses and 24/122 (19.7%) had partial responses. There were no significant differences between complete or partial response in the low- and high-dose groups.

**IFN efficacy based on HCV RNA (Table 3)**

In 68 patients, the HCV RNA level was assayed immediately before starting IFN administration, at the completion of IFN administration, and 6 months after completing IFN administration. As shown in Table 3, 19/68 (27.9%) patients had a HCV-negative complete response, and 10/68 (14.7%) had a HCV-positive complete response. There were no significant differences between the low- and high-dose groups.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patients' clinical characteristics and laboratory findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td>Low dose</td>
</tr>
<tr>
<td>No. of patients</td>
<td>21</td>
</tr>
<tr>
<td>Male: Female</td>
<td>10:11</td>
</tr>
<tr>
<td>Age (yrs, mean±SD)</td>
<td>52.4±10.8</td>
</tr>
<tr>
<td>Interval after blood transfusion (yrs, mean±SD)</td>
<td>18.7±12.2</td>
</tr>
<tr>
<td>Serum ALT before therapy (IU/l, mean±SD)</td>
<td>92.4±64.5</td>
</tr>
<tr>
<td>Serum albumin before therapy (g/dl, mean±SD)</td>
<td>4.1±0.4</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Evaluation of ALT response in the interferon-treated chronic hepatic C patients with a history of blood transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td>Low dose (n=21)</td>
</tr>
<tr>
<td>Complete response (%)</td>
<td>9 (42.9)</td>
</tr>
<tr>
<td>Partial response (%)</td>
<td>3 (14.3)</td>
</tr>
<tr>
<td>No change (%)</td>
<td>9 (42.9)</td>
</tr>
</tbody>
</table>
Table 3 Evaluation of HCV RNA and ALT response in the interferon-treated chronic hepatitis C patients with a history of blood transfusion

<table>
<thead>
<tr>
<th>Response</th>
<th>Low dose (n=11)</th>
<th>High dose (n=57)</th>
<th>Total (n=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV RNA-negative Complete response (%)</td>
<td>4(36.4)</td>
<td>15(26.3)</td>
<td>19(27.9)</td>
</tr>
<tr>
<td>HCV RNA-positive Complete response (%)</td>
<td>2(18.2)</td>
<td>8(14.0)</td>
<td>10(14.7)</td>
</tr>
<tr>
<td>HCV RNA-positive Partial response and no change (%)</td>
<td>5(45.4)</td>
<td>34(59.6)</td>
<td>39(57.4)</td>
</tr>
</tbody>
</table>

Table 4 Relationship between IFN efficacy and duration of clinical HCV infection

<table>
<thead>
<tr>
<th>Response</th>
<th>Interval after blood transfusion(years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1~9</td>
</tr>
<tr>
<td>HCV RNA-negative Complete response (%)</td>
<td>9(40.9)</td>
</tr>
<tr>
<td>HCV RNA-positive Complete response (%)</td>
<td>2(9.1)</td>
</tr>
<tr>
<td>HCV RNA-positive Partial response and no change (%)</td>
<td>11(50.0)</td>
</tr>
</tbody>
</table>

Patients with an interval after blood transfusion of less than 20 years had significantly higher rates of HCV RNA-negative complete response than those with an interval of 20 years or more (Wilcoxon's rank sum test, p<0.039)

Fig. 1 Relationship between the interval between the time of blood transfusion and the time of liver biopsy and scoring the stage of hepatic fibrosis. A significant positive correlation was observed between the period and the score for the stage of hepatic fibrosis. (Spearman's rank correlation p<0.001, R=0.316)
Duration of Chronic HCV Infection and Efficacy of IFN

high-dose groups.

**IFN efficacy and interval after blood transfusion**

Table 4 summarizes the relationship between IFN efficacy and the interval between blood transfusion and the start of IFN therapy. Patients with an interval of less than 20 years had significantly higher rates of HCV RNA-negative complete response than those with an interval of 20 years or more (p < 0.05).

**Relationship between IFN efficacy and liver histopathology**

We analyzed the relationship between IFN efficacy and the histological parameters, including staging and grading score and the four histological features. There was no significant relationship between IFN efficacy and the histopathological parameters. We also examined the relationship between interval between blood transfusion and the time of the liver biopsy and the histological parameters. A significant positive correlation was observed between the interval and the score for the stage of hepatic fibrosis as shown Fig. 1.

**Discussion**

IFN therapy in chronic hepatitis C patients was first reported by Hoofnagle et al.\(^{1}\) and has recently been found to inhibit the development of liver cancer.\(^{17}\) Others have reported\(^{19-12}\) that virus and host factors play an important role in IFN efficacy in chronic hepatitis C patients. Host factors, including the progression of liver disease, especially hepatic fibrosis, are particularly critical.\(^{11,12}\)

It was also reported that the HCV RNA hypervariable region I (HVRI) varies as the infection persists\(^{18}\) and that serum HCV RNA levels increase as the liver pathology progresses and the duration of chronic HCV infection grows longer.\(^{19,20}\) The duration of chronic HCV infection may depend on both viral and host factors. Although it is difficult to know the precise duration of chronic HCV infection, many patients are infected with HCV through blood transfusion. Therefore, to investigate the correlation between IFN efficacy and chronic HCV infection period, we studied patients with chronic hepatitis C having an accurate documented history of blood transfusion.

Patients who were HCV RNA-negative and had a normal ALT level after the completion of IFN therapy usually had shorter periods of chronic HCV infection.

With regard hepatic fibrosis, the patients with a longer duration of chronic HCV infection had more significant progression than the patients with a shorter period (p < 0.0001, R = 0.316). However, there was no correlation between the stage of hepatic fibrosis and IFN efficacy. These findings indicate that IFN efficacy does not depend on hepatic fibrosis alone. Pretreatment HCV RNA level and HCV genotype may influence efficacy, and IFN-resistant HCV awaits further examination.

Conclusions concerning the relationship between serum HCV RNA level and histological progression still controversial.\(^{19,20}\) The relationship between serum HCV RNA level and IFN efficacy cannot be explained by viral factors alone. For example, reports\(^{19,20}\) show that HCV RNA levels rise as the duration of chronic HCV infection and the stage of liver disease increase. Another report\(^{21}\) claims that patients with chronic active hepatitis having advanced fibrosis have decreased HCV RNA levels. Thus, it has been difficult to find strict associations between IFN efficacy and individual factors, because they change with time.

IFN is reported to have excellent therapeutic efficacy in patients with acute hepatitis C,\(^{22,23}\) which coincides with our findings in patients with a shorter duration of HCV infection.

Recently we tried to clarify the decrease in IFN efficacy in a rat model of liver cirrhosis. There was lower induction of 2',5'-oligoadenylate synthetase activity in the hepatocytes of the rats with liver cirrhosis than in the control rats. This may mean that sufficient IFN could not reach the hepatocytes.\(^{24,25}\) Results of the present study suggest that IFN therapy should be started as soon as
possible after a patient has evidence of HCV infection.

Acknowledgments

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References

輸血歴のある C 型慢性肝炎患者における HCV 感染
持続期間と IFN 治療効果との関連

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九州地区肝炎治療研究会

要 旨
九州地区64施設の共同研究によって、輸血歴のある C 型慢性肝炎患者122例を対象にして、IFN の治療効果が C 型肝炎ウイルス (HCV) の感染持続期間に関連があるか否かを検討した。輸血から IFN 治療開始までの期間が20年以下の群には、以上の群よりも治療後の HCV RNA 陰性化を伴った ALT 値の持続正常化例が有意 (p<0.039) に多く認められた。今回の研究結果は、HCV の感染持続期間と IFN の治療効果には関連性があり、感染後早期に治療を開始した方がより治療効果が得られ易いことを示唆している。