Collaboration between Hepatologists and Primary Care Physicians in Treating Patients with Chronic Hepatitis C

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Abstract

**Objective:** The purpose of this study was to assess the treatment outcome in patients with chronic hepatitis C (CHC) using the current standard antiviral therapy when patients were treated in collaboration between hepatologists and primary care physicians (PCPs).

**Patients and Methods:** One hundred and ten patients with CHC were treated with a combination therapy of peginterferon-alpha 2b and ribavirin. Among them, 25 patients were treated by a collaboration between hepatologists and PCPs (collaboration group), whereas 85 patients were treated with exclusively by hepatologists (noncollaboration group). The duration of the therapy was 48 weeks for 58 ‘difficult-to-treat’ patients (genotype 1 with a high load of HCV-RNA; 1H patients) and 24 weeks for the remaining 52 patients (non-1H patients). In the collaboration group, antiviral therapy was initiated and adjusted, if needed, by hepatologists (visits every four weeks), whereas the weekly administration of peginterferon-alpha 2b was performed by PCPs. Clinical characteristics and the treatment outcome were compared between these two groups.

**Results:** The two groups had similar baseline characteristics. By intention to treat, the two groups showed similar rates of treatment-related serious adverse effects (0% vs. 1%, respectively) and dropout rates for adverse effects (8% vs. 13%, respectively). Sustained virologic response rates were also similar between the two groups, being 42% vs. 39% in the 58 1H patients (NS) and 62% vs. 64% in the 52 non-1H patients (NS), respectively.

**Conclusions:** Collaboration between hepatologists and PCPs may be a valid treatment alternative to treat patients with CHC using the current standard antiviral therapy.

**Key words:** chronic hepatitis C, peginterferon, ribavirin, primary care physician, collaboration

Introduction

Hepatitis C virus (HCV) infection is the leading cause of hepatocellular carcinoma (HCC) in Japan. For this reason, the medical community and the Japanese Government have made it a priority to offer all Japanese patients with chronic hepatitis C (CHC) the option of antiviral therapy. The current standard therapy is a combination of pegylated interferon and ribavirin (RBV)\textsuperscript{6).} High response to the combination therapy has been reported by large clinical trials\textsuperscript{2–5),} in which patients were closely managed by hepatologists and treatment compliance was high. The management of treatment-related adverse effects requires experience and expertise\textsuperscript{6).} In real life, however, most patients with CHC are treated by primary care physicians (PCPs)\textsuperscript{7).} Treatment by specialists could improve the therapy outcome. However, there are a few hepatologists (3.4/100,000 population) in Japan, and this is the case especially in Ibaraki prefecture (2.3/100,000 population), which is where Tsuchiura city is located. Few studies have assessed whether a collaboration between hepatologists and PCPs is a valid treatment alternative to treat patients with CHC. The purpose of this study was to assess the treatment outcome in patients with CHC using the current standard antiviral therapy when patients were treated in collaboration between hepatologists and PCPs.

Patients and Methods

Between May 2005 and July 2008, 110 Japanese patients with CHC were treated with a combination therapy of peginterferon-alpha 2b and ribavirin at Tsuchiura Kyodo General Hospital (TKGH), Tsuchiura, Japan. Among them, 25 patients were treated by a collaboration between hepatologists and PCPs (collaboration group), whereas 85 patients were treated exclusively by hepatologists (noncollaboration group). All patients were positive for both anti-HCV antibody by a third-generation enzyme immunoassay and HCV-
RNA at the start of treatment and showed elevated serum alanine transaminase (ALT; above the upper limit for the normal) for the past 6 months. Exclusion criteria included decompensated liver disease, coexisting serious medical or psychiatric illness, other forms of liver disease (drug-induced liver disease, alcoholic liver disease, autoimmune hepatitis), a neutrophil count less than 1500/mm³, a platelet count less than $8 \times 10^4$/mm³, a hemoglobin of less than 12 g/dL, a serum creatinine greater than 1.5 times the upper limit of the normal range and co-infection with hepatitis B virus or human immunodeficiency virus. The duration of the therapy was 48 weeks for ‘difficult-to-treat’ patients (genotype 1 with a high load of HCV-RNA; 1H patients) and 24 weeks for the remaining patients (non-1H patients). In the 1H patients, however, therapy was discontinued if HCV-RNA was still detectable at week 24. All patients were treated with PegIFNa2b (1.5 μg/kg subcutaneously) once weekly plus RBV at a dose adjusted for body weight (patients over 80 kg of weight received 1000 mg, those weighing from 60–80 kg received 800 mg and those under 60 kg received 600 mg). Safety assessment included red blood cell, white blood cell and platelet counts in response to therapy. PegIFNa2b was reduced to half of the original dose in patients with $<750$/mm³ neutrophils, whereas it was withdrawn if platelet counts fell below $8 \times 10^4$/mm³, a hemoglobin of less than 12 g/dL, a serum creatinine greater than 1.5 times the upper limit of the normal range and co-infection with hepatitis B virus or human immunodeficiency virus. The duration of the therapy was 48 weeks for ‘difficult-to-treat’ patients (genotype 1 with a high load of HCV-RNA; 1H patients) and 24 weeks for the remaining patients (non-1H patients). In the 1H patients, however, therapy was discontinued if HCV-RNA was still detectable at week 24. All patients were treated with PegIFNa2b (1.5 μg/kg subcutaneously) once weekly plus RBV at a dose adjusted for body weight (patients over 80 kg of weight received 1000 mg, those weighing from 60–80 kg received 800 mg and those under 60 kg received 600 mg). Safety assessment included red blood cell, white blood cell and platelet counts in response to therapy. PegIFNa2b was reduced to half of the original dose in patients with $<750$/mm³ neutrophils, whereas it was withdrawn if platelet counts fell below $8 \times 10^4$/mm³, whereas PegIFNa2b was withdrawn when the threshold of $5 \times 10^4$/mm³ was reached. The RBV dose was tapered by 200 mg/day in patients with hemoglobin $<10$ g/dL, whereas it was discontinued in patients with hemoglobin $<8.5$ g/dL. The safety assessment also included other treatment-related adverse effects. A posttreatment follow-up period of 24 weeks was also included in the study. Liver biopsy was not performed prior to the study.

When both the patient and the PCP wished, the therapy was done in collaboration between a hepatologist and the PCP. Otherwise, the therapy was done exclusively by hepatologists at TKGH. There were 25 patients in the collaboration group. Hepatologists initiated the antiviral therapy and carefully monitored tolerability during the first four weeks of treatment. Thereafter, the weekly administration of PegIFNa2b was performed by the PCP after a careful examination in an interview and/or physical examination. Blood tests were not performed unless side effects such as hypothyroidism were suspected. PCPs performed symptomatic treatment if needed. PCPs had been recommended to consult hepatologists if needed. Only hepatologists decided whether to discontinue the therapy. The doses of PegIFNa2b and/or RBV were adjusted, if needed, by hepatologists every four weeks at TKGH at the time of routine laboratory tests, including HCV-RNA determinations. In the non-collaboration group, on the other hand, 85 patients were exclusively treated by hepatologists weekly at TKGH. The doses of PegIFNa2b and/or RBV were adjusted, if needed, by hepatologists at least every four weeks at the time of routine laboratory tests, including HCV-RNA determinations. Additional laboratory tests were performed by hepatologists when needed.

The serum HCV RNA level was measured with a quantitative HCV RNA assay (Cobas Amplicore HCV monitor ver. 2.0; Roche Diagnostic Systems, Tokyo, Japan) during, and after therapy. The range of the assay was 0.5 to 500 KIU/mL. When the measured serum HCV RNA level was lower than 0.5 KIU/mL, HCV RNA was also determined by a quantitative PCR assay (Ampliplex HCV v2.0®, Roche Diagnostic Systems, Tokyo, Japan), which had a detection limit of 50 IU/mL. A high viral load was defined as a serum HCV-RNA level of more than 100 KIU/mL serum. HCV genotyping was assayed by ELISA®. Assessment of efficacy was based on sustained virologic response (SVR), i.e., undetectable HCV-RNA at week 24 post treatment. Informed consents were obtained from all patients. Clinical characteristics and the treatment outcome were compared between these two groups.

Values were expressed as means ± SD. The Mann-Whitney U test or Fisher’s exact probability test was used for statistical analyses, and P values less than 0.05 were considered statistically significant. Patients who discontinued treatment for any reason were categorized as nonresponders (intention-to-treat analysis).

**Results**

In the collaboration group, we collaborated with 12 PCPs as nonhepatologist. Twenty-three patients were referred to a hepatologist by the PCPs. Among them, eleven patients had been cared for underlying diseases by their PCPs. The remaining two patients were referred to PCPs by a hepatologist for the patients’ convenience. The distance from TKGH to the office of the PCPs varied between 2.5-25.3 (12.7 ± 6.2) km.

The baseline characteristics of the 1H patients are shown in Table 1. No significant difference was present between the collaboration group and the noncollaboration group except for an underlying disease. Diabetes mellitus was more frequently seen in the noncollaboration group. The baseline characteristics of the non-1H patients are shown in Table 2. No significant difference was present between the two groups except for HCV genotypes and baseline ALT levels. In the collaboration group, the HCV genotype was 1 in two patients and 2 in the remaining 11 patients. In the noncollaboration group, all patients were infected with HCV genotype 2.
The safety and tolerability profile of the 1H patients is shown in Table 3. Serious adverse effects (cerebral hemorrhage) occurred in one patient belonging to the noncollaboration group. Therapy was discontinued because HCV-RNA was still detectable at week 24 in one patient of the collaboration group and four patients of the noncollaboration group. Therapy was discontinued for safety reasons in one patient (depression) of the collaboration group and nine patients of...
the noncollaboration group (cerebral hemorrhage, n=1; depression, n=2; GI symptoms, n=1; psychiatric symptoms, n=3; retinopathy, n=1; and dermatologic symptoms, n=1). Therapy was discontinued for reasons other than safety in four patients of the noncollaboration group (lost to follow-up, n=3; economic reason, n=1). Other adverse effects are shown in Table 3. The number of blood tests performed was 15.8 ± 3.6 in the collaboration group and 18.8 ± 4.3 in the noncollaboration group (P=0.0517). No significant difference was present between the 2 groups in the rates of hematologic toxicities. The rates of the dose reduction of PegIFNa2b and RBV were also comparable between the two groups. As a result, 6/12 (50.0%) patients of the collaboration group and 14/46 (30.4%) patients of the noncollaboration group received ≥ 80% of the recommended dosage of both PegIFNa2b and RBV for ≥ 80% of the intended duration of therapy (P=0.3065).

The safety and tolerability profile of the non-1H patients is shown in Table 4. No serious adverse event was observed. Therapy was discontinued for safety reasons in one patient (dermatologic symptoms) of the collaboration group and three patients of the noncollaboration group (depression, n=2, GI symptoms, n=1). Therapy was discontinued for reasons other than safety (lost to follow-up) in one patient of the collaboration group and two patients of the noncollaboration group. Other adverse effects are shown in Table 4. The number of blood test performed was 8.0 ± 1.8 in the collaboration group and 13.4 ± 4.8 in the noncollaboration group (P=0.0004). No significant difference was present between the two groups in the rates of hematologic toxicities. As a result, the rates of the dose reduction of PegIFNa2b and RBV were also comparable between the two groups.

Treatment responses of the patients in the intention-to-treat analysis are shown in Table 5. For the 1H patients, the SVR rate in the collaboration group was 42%, which was similar to that (39%) in the noncollaboration group. For the noncollaboration group, the SVR rate in the collaboration group was 62%, which was also similar to that (64%) in the noncollaboration group.

**Discussion**

In Japan, the death rate from HCCs has been increasing\(^9\). This increase is mostly attributed to chronic HCV infection.

### Table 3  Rates of safety and tolerability in the 1H patients

|                                | Collaboration group (n=12) | Noncollaboration group (n=46) | P value |
|--------------------------------|----------------------------|------------------------------|---------|
| Serious adverse events, n (%)  | 0                          | 1 (2)                        | >.9999  |
| Treatment modification, n (%)  |                            |                              |         |
| Discontinuation for 24 weeks rule\(^a\) | 1 (8)                     | 4 (7)                        | >.9999  |
| Discontinuation for safety reasons | 1 (8)                     | 9 (20)                       | 0.6700  |
| Discontinuation for reasons other than safety | 0                      | 4 (7)                        | 0.5707  |
| Completed therapy, n (%)       | 10 (80)                    | 29 (63)                      | 0.3018  |
| Depression, n                  | 1                          | 2 (4)                        | 0.5080  |
| Other adverse effects, n (%)   |                            |                              |         |
| Influenza-like syndrome        | 7 (58)                     | 24 (52)                      | 0.7556  |
| Gastrointestinal symptoms      | 1 (8)                      | 1 (2)                        | 0.3739  |
| Psychiatric symptoms           | 0                          | 3 (7)                        | >.9999  |
| Dermatologic symptoms          | 5 (42)                     | 18 (39)                      | >.9999  |
| Retinopathy                    | 0                          | 1 (2)                        | >.9999  |
| Hematologic effect, n (%)      |                            |                              |         |
| Anemia (8.5 g/dL ≤Hb<10 g/dL)  | 6 (50)                     | 16 (35)                      | 0.5053  |
| Anemia (Hb<8.5 g/dL)           | 0                          | 1 (2)                        | >.9999  |
| Neutropenia <750/mm\(^3\)     | 2 (17)                     | 9 (20)                       | >.9999  |
| Neutropenia <500/mm\(^3\)     | 0                          | 4 (7)                        | 0.5707  |
| Thrombocytopenia <8 × 10\(^4\)/mm\(^3\) | 4 (33)                 | 11 (24)                      | 0.4677  |
| Thrombocytopenia <5 × 10\(^4\)/mm\(^3\) | 0                    | 0                             | >.9999  |
| PegIFNa2b dose reduction, n (%)| 5 (42)                     | 22 (48)                      | 0.7556  |
| RBV dose reduction, n (%)      | 8 (67)                     | 24 (52)                      | 0.5178  |

\(^a\)Therapy was discontinued because HCV-RNA was still detectable at week 24.
To reduce the deaths from HCC, a national 5-year project identifying HCV carriers in the general Japanese population was started in April 2002\(^9\). As part of a regular preventive physical examination program, offered every five years to subjects 40 years and older, HCV testing was performed. Additionally, HCV testing was also offered to individuals with increased risk of HCV infection. During the first year, the project detected HCV RNA in 1.1% of subjects tested during their regular physical examination and in 2.7% of the high-risk individuals. Among the newly diagnosed HCV-positive patients, a considerable proportion (48%) had visited nonhepatologist such as their PCPs\(^9\). However, most PCPs have limited experience in treating patients with CHC with an interferon-based therapy. Therefore, supervision by a specialist could improve treatment outcome. Japan has relative few hepatologists, and this is especially the case in Ibaraki Prefecture, where TKGH is located. Collaboration between hepatologists and PCPs is therefore desirable.

Additionally, self-injection of PegIFNa2b is not permitted in Japan, and weekly injections in a PCP’s office are more convenient for patients.

To our knowledge, this is the first study to assess an interferon-based therapy in patients with CHC managed in collaboration between hepatologist and PCPs, although the sample size is small. The current standard therapy uses a combination of pegylated interferon and RBV. The du-

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**Table 4** Rates of safety and tolerability in the non-1H patients

|                              | Collaboration group (n=13) | Noncollaboration group (n=39) | P value |
|------------------------------|---------------------------|-------------------------------|---------|
| Serious adverse events, n (%) 0 | 0                         | >.9999                        |
| Treatment modification, n (%) 1 (8) | 2 (5)                     | >.9999                        |
| Discontinuation for safety reasons 1 (8) | 3 (8)                     | >.9999                        |
| Discontinuation for reasons other than safety 1 (8) | 2 (5)                     | >.9999                        |
| Completed therapy, n (%) 11 (84) | 34 (87)                   | >.9999                        |
| Depression, n 0                | 2 (5)                     | >.9999                        |
| Other adverse effects, n (%)    |                           |                               |
| Influenza-like syndrome 5 (38) | 14 (36)                   | >.9999                        |
| Gastrointestinal symptoms 0    | 1 (3)                     | >.9999                        |
| Psychiatric symptoms 1 (8)     | 0                         | 0.2500                        |
| Dermatologic symptoms 4 (31)  | 13 (33)                   | >.9999                        |
| Hematologic effect, n (%)      |                           |                               |
| Anemia (8.5 g/dL < Hb < 10 g/dL) 2 (15) | 6 (15)                   | >.9999                        |
| Anemia (Hb < 8.5 g/dL) 0       | 1 (3)                     | >.9999                        |
| Neutropenia < 750/mm\(^3\) 0  | 6 (15)                    | 0.3172                        |
| Neutropenia < 500/mm\(^3\) 0  | 0                         | 0.9999                        |
| Thrombocytopenia < 8 \times 10\(^3\)/mm\(^3\) 0 | 7 (18)                    | 0.1715                        |
| Thrombocytopenia < 5 \times 10\(^3\)/mm\(^3\) 0 | 0                        | >.9999                        |
| PegIFNa2b dose reduction, n (%) 1 (8) | 13 (33)                   | 0.1554                        |
| RBV dose reduction, n (%)      3 (23) | 18 (46)                   | 0.1977                        |

**Table 5** Treatment responses of the patients in the intention-to-treat analysis

|                          | Collaboration group (n=13) | Noncollaboration group (n=39) | P value |
|--------------------------|---------------------------|-------------------------------|---------|
| 1H patients              |                           |                               |
| Total number of patients 12 | 46                        | >.9999                        |
| SVR, n (%) 5 (42)        | 18 (39)                   | >.9999                        |
| Non-1H patients          |                           |                               |
| Total number of patients 13 | 39                        | >.9999                        |
| SVR, n (%) 8 (62)        | 25 (64)                   | >.9999                        |

SVR, sustained virologic response.
ation of therapy and response to therapy are HCV genotype-specific. Genotype 1 patients require 48 weeks of the combination therapy for 50% successful viral elimination, while genotype 2 patients require 24 weeks of therapy for 80% or 90% viral elimination\(^2\)\(^-\)\(^9\). In the present study, the two groups showed similar rates of treatment-related serious adverse effects and dropout rates for adverse effects. SVR rates were also similar between the two groups. Moreover, for the 1H patients, the SVR rate (intention-to-treat analysis) in the collaboration group was 42%, which was similar to that (121/254, 48%) reported in a large clinical trial\(^8\), where the patients were managed completely by hepatologists \((P=0.7781)\). The results also showed a similar discontinuation rate \((1/12, 8\% \text{ vs. } 52/254, 20\%, P=0.4689)\) and safety profile. Among the non-1H patients, 11 patients were infected with HCV genotype 2. For the genotype 2 patients, the SVR rate (intention-to-treat analysis, 8/11, 73%) was also similar to that \((168/250, 67\%)\) obtained in a large clinical trial \([5]\) \((P>0.9999)\). The rate of therapy discontinuation \((1/11, 9\%, \text{ vs. } 37/250, 15\%, P>0.9999)\) and the safety profile were also comparable.

In a retrospective study\(^9\)^\(^b\), significantly better treatment response rates were found in those patients who visited a specialist regularly, at least every three months, compared with those who visited a specialist irregularly. That study also suggested that ‘difficult to treat’ patients, i.e., those infected with HCV genotypes 1 and 4, may benefit more from close therapy supervision by a specialist to achieve treatment success rates. Treatment interruptions/discontinuations occurred significantly more often in “irregular visitors” compared with “regular visitors.” Treatment success is highly influenced by adherence to therapy in genotype-1-infected patients\(^9\). As the authors mentioned, therapy-associated adverse effects may lead, in the absence of a specialist, to more premature dose reductions and/or unnecessary treatment discontinuations. In the present study, the adherence to the therapy in the 1H patients was comparable between the two groups. Moreover, the discontinuation rate in the collaboration group was low and similar to that in the non-collaboration group. The low discontinuation rates in the collaboration group could contribute to the comparable SVR rates to those reported in the large clinical trials. In the present study, the hepatologists supervised treatment of the patients every four weeks. Whether supervision by hepatologists every four weeks is superior to that done every 3 months needs to be assessed. Large-scale studies are also needed to confirm the usefulness of the collaboration between hepatologists and PCPs.

In conclusion, collaboration between hepatologists and primary care physicians may be a valid treatment alternative to treat patients with chronic hepatitis C using current standard antiviral therapy.

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