Clinical characteristics of null responders to Peg-IFNα2b/ribavirin therapy for chronic hepatitis C

Hideyuki Suzuki, Satoru Kakizaki, Norio Horiguchi, Takeshi Ichikawa, Ken Sato, Hitoshi Takagi, Masatomo Mori

Hideyuki Suzuki, Satoru Kakizaki, Norio Horiguchi, Takeshi Ichikawa, Ken Sato, Hitoshi Takagi, Masatomo Mori, Department of Medicine and Molecular Science, Gunma University Graduate School of Medicine, Maebashi, Gunma 371-8511, Japan

Author contributions: Suzuki H and Kakizaki S, designed the study, analyzed and interpreted data, and drafted the manuscript; Horiguchi N, Ichikawa T, Sato K, and Takagi H, treated the patients and provided clinical data and performed the liver biopsy; and Mori M, supervised the work.

Correspondence to: Satoru Kakizaki, MD, PhD, Department of Medicine and Molecular Science, Gunma University Graduate School of Medicine, 3-39-15 Showa-machi, Maebashi, Gunma 371-8511, Japan. kakizaki@showa.gunma-u.ac.jp

Telephone: +81-27-2208127 Fax: +81-27-2208136

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Abstract

AIM: To predict which chronic hepatitis C patients are likely to be late-responders, we herein investigated the clinical characteristics of null-responders at 36 wk with hepatitis C virus (HCV) genotype Ib and a high viral load during the course of pegylated interferon (Peg-IFN)/ribavirin therapy.

METHODS: One hundred forty-two patients with genotype Ib HCV and a high viral load were included in this study. Peg-IFNα2b (1.5 µg/kg once a week) and ribavirin (600-1000 mg per day according to body weight) were administered for 48 wk. We defined null-responders as the cases that never cleared serum HCV RNA as determined using RT-PCR until 36 wk. Other patients were defined as responders. We compared the clinical characteristics (age, gender, body mass index, previous treatment) and HCV RNA titer during the therapy between null-responders and responders.

RESULTS: The HCV RNA clearance rate was 17.9% (24/134), 46.3% (62/134), 60.6% (86/142), 86.6% (123/142), and 88.0% (125/142) at 4, 8, 12, 24, and 36 wk, respectively. There were 17 patients (12.0%) who were still null-responders at 36 wk. There were no differences in the clinical characteristics between the responders and null-responders except for the titer and decline rates of HCV RNA at 1 wk and 4 wk. The HCV RNA titers at 1 wk and after 4 wk of treatment were significantly higher in the null-responders in comparison to the responders (P <0.01). The serum HCV RNA titers of the responders decreased by 1.3 log after 1 wk of treatment, and 1.6 log after 4 wk of treatment, respectively. On the other hand, the titers of the null responders decreased by only 0.5 log after 1 wk, and 0.7 log after 4 wk of treatment, respectively. The decrease rates of HCV RNA after 1 and 4 wk of treatment were significantly worse for null responders than for the responders (P <0.01).

CONCLUSION: The HCV RNA titer at 1 wk and 4 wk after initiating treatment may be useful for predicting null-responders to Peg-IFNα2b/ribavirin therapy. However, further investigation is needed to determine the optimal time at which the decision to discontinue the Peg-IFNα2b/ribavirin therapy for null-responders can be made.

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Key words: Null responder; Pegylated interferon α2b; Ribavirin; Chronic hepatitis C

Peer reviewers: Qiang Liu, PhD, Vaccine and Infectious Disease Organization, University of Saskatchewan, 120 Veterinary Road, Saskatoon, Saskatchewan, S7N 5E3, Canada; Emmanouil Sinakos, MD, Aristotle University of Thessaloniki, 11A, Perdika Str., Pilea 55535, Greece; Toru Ishikawa, MD, Department of Gastroenterology, Saiseikai Niigata Second Hospital, Teraji 280-7, Niigata 950-1104, Japan
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INTRODUCTION

Chronic hepatitis C is a major cause of liver cirrhosis and hepatocellular carcinoma[1,2]. Improvements in antiviral therapy for patients with hepatitis C virus (HCV) infection have recently been achieved by means of the use of pegylated interferon (Peg-IFN) combined with ribavirin[3,4], and this treatment strategy has become a standard therapy for the eradication of HCV infection. However, the sustained virological response (SVR) rates in patients with HCV genotype 1 and a high viral load are still insufficient, and the search continues for better treatment strategies. The treatment of patients with HCV genotype 1 with Peg-IFN and ribavirin for more than 48 wk has led to higher SVR rates. Although many studies have extended the duration of therapy from 48 wk to 72 wk, the optimal duration has not yet been determined.

In the 2008 Japanese guidelines for the treatment of patients with chronic hepatitis C[5], treatment with Peg-IFN combined with ribavirin for 48 wk is indicated for treatment-naïve patients infected with genotype 1 HCV. Treatment is recommended to be continued for an additional 24 wk (72 wk total) in the patients who remained positive for HCV RNA (detectable by the real-time polymerase chain reaction) at 12 wk after the start of treatment, but who become negative for HCV RNA after 13-36 wk of treatment[6]. As a result, the prolonged treatment of the patients who still have evidence of HCV infection at 36 wk is not indicated when the normalization of the alanine aminotransferase (ALT) level is not achieved. Because Peg-IFN/ribavirin has many adverse effects, the patients who are null responders should cease the treatment and wait until commencing a new treatment regimen which includes protease inhibitors. It would therefore be useful to predict null responders earlier in the course of the treatment in order to both avoid adverse effects, and to achieve better disease control. We herein describe our investigation of the clinical characteristics of null-responders to Peg-IFN with ribavirin therapy with HCV genotype Ib and a high viral load.

MATERIALS AND METHODS

Patients

One hundred forty-two patients with chronic hepatitis C were included in this study. All patients fulfilled the following inclusion criteria: (1) HCV genotype Ib; (2) more than 10^5 copies/mL of HCV in the serum; and (3) an elevated serum ALT level for least 6 mo before initiation of treatment. In addition to these criteria, patients were excluded when they suffered from any of the following conditions: (1) decompensated liver disease; (2) other causes of liver disease such as hepatitis B infection; (3) autoimmune disorders; (4) hemoglobin value < 11 g/dL; (5) white blood cell count < 3 000/μL; (6) thrombocytopenia < 70 000/μL; (7) neoplastic disease; (8) severe cardiac disease; (9) other severe concurrent diseases such as pre-existing psychiatric conditions; or (10) pregnancy or lactation. Informed consent was obtained from all patients enrolled in the study, after a thorough explanation of the aims, risks and benefits of this therapy.

Study design

One hundred forty-two patients received Peg-IFNα2b/ribavirin therapy from December 2005 to July 2006 at Gunma University Hospital and its affiliated hospitals. Patients received Peg-IFNα2b (1.5 μg/kg once a week; Schering-Plough, Tokyo), and 600 mg, 800 mg or 100 mg ribavirin per day orally, adjusted according to body weight (600 mg for weight under 60 kg, 800 mg for weight between 60 kg and 80 kg, 1000 mg for weight over 80 kg) for 48 wk. The patients were followed-up for another 24 wk after the treatment, i.e. until week 72. Clinical characteristics including age, gender, body mass index, and previous treatment, were analyzed. Serum biochemistry and the HCV RNA titer were measured at pre-treatment and after 4, 8, 12, 24, 36, 48, and 72 wk of treatment. We defined as “null-responders” the cases that did not clear serum HCV RNA (assessed using RT-PCR) by 36 wk. Other patients were defined as “responders”. A sustained virological response (SVR) was defined as undetectable HCV RNA in serum after 24 wk of treatment. All the other patients whose HCV RNA was positive at 24 wk after the end of treatment were classified as non-SVR.

Histopathological examination of the liver

A liver biopsy was performed for patients who agreed, after an explanation of the aim and risks before treatment. Hepatic inflammation (grade) and fibrosis (stage) were assessed by the semiquantitative histological score proposed by Scheuer[7] and Desmet et al[8]. The amount of portal/peripoortal inflammatory activity, lobular inflammatory activity, and degenerative liver cell changes were scored, using a scale of 0 to 3 for the criterion ‘inflammatory activity’ (0: absent; 1: mild; 2: moderate; 3: severe). The degree of fibrosis was scored using a scale of 0 to 4 (0: absent; 1: mild without septa; 2: moderate with few septa; 3: numerous septa without cirrhosis; 4: cirrhosis).

Statistical analysis

Fisher’s exact probability test for frequency tables was used for statistical analysis. Distributions of continuous variables were analyzed by the Mann-Whitney U-test. P value < 0.05 was considered significant.

RESULTS

Clinical characteristics and response to therapy

Patients’ characteristics are shown in Table 1. The male:
female ratio was 80:62. The mean patient age was 56.0 ± 10.0 years old (range 19-71). Mean body mass index was 25.3 ± 3.0 kg/m². Ninety-seven patients were naïve for IFN treatment, and 45 patients had received previous treatment. Eighty-eight patients underwent a liver biopsy. Inflammatory activity was classified as A0: 0; A1:32; A2: 54; and A3: 2 patients, and the fibrosis score was F0: 4; F1: 30; F2: 28; F3: 21; and F4: 5 patients, respectively. At the end of the study (72 wk), the overall SVR rate of all patients was 60/142 (42.3%), that of responders was 60/125 (48.0%) and that of null responders was 0/17 (0.0%).

Factors associated with a null response

There were 17 patients (12.0%) who were null-responders at 36 wk. A comparison of the clinical characteristics between the responders and null-responders is shown in Table 2. There were no significant differences between responders and null-responders with regard to gender, age, body weight, body mass index, previous treatment with IFN, baseline HCV RNA levels, serum ALT levels, or stage of fibrosis (Table 2). However, the HCV RNA levels at 1 wk and 4 wk after initiating treatment were significantly higher in null-responders compared with responders. Furthermore, the decrease rates of HCV RNA after 1 and 4 wk of treatment were significantly worse for null responders than for the responders. These results seem to be reasonable, because null responders had little or no decrease in their HCV RNA titer. The probability of SVR is also dependent on the speed of the decline in the viral load. A faster HCV RNA decline to an undetectable level means longer duration viral suppression, which can be translated to a higher chance of SVR. A large combined dataset including 569 genotype 1 HCV infected patients treated by Peg–IFNα2b/ribavirin therapy, further studies are needed to confirm our findings and to identify other useful predictive factors.

In the present study, the null response was not associated with gender, age, or previous IFN therapy. With on treatment. Based on these guidelines, the patients who are positive for HCV infection after 36 wk of treatment are not recommended for prolonged therapy, and should cease the treatment when the normalization of the ALT level is not achieved. We conducted this study to determine whether it is possible to predict which patients will be non-responsive to the treatment.

There were no significant differences in the clinical characteristics between the responders and null-responders, except for the titer and decline rates of HCV RNA at 1 wk and 4 wk respectively after starting treatment. HCV RNA titers after 1 wk and 4 wk of treatment were significantly higher in null-responders compared with responders. Furthermore, the decrease rates of HCV RNA after 1 and 4 wk of treatment were significantly worse for null responders than for the responders. These results seem to be reasonable, because null responders had little or no decrease in their HCV RNA titer. The probability of SVR is also dependent on the speed of the decline in the viral load. A faster HCV RNA decline to an undetectable level means longer duration viral suppression, which can be translated to a higher chance of SVR. A large combined dataset including 569 genotype 1 HCV infected patients treated by Peg–IFNα2b/ribavirin therapy, further studies are needed to confirm our findings and to identify other useful predictive factors.

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### Table 1: The characteristics of patients with chronic hepatitis C treated by pegylated interferon/ribavirin therapy

| Characteristics | Number of patients n | Responders | Null responders |
|-----------------|----------------------|------------|----------------|
| Number of patients | 142 | 123 | 17 |
| Gender | Male; Female | 80.62 | 70; 53 |
| Mean age (range) | Years | 56.0 ± 10.0 (19-71) | 56.3 ± 10.2 | 57.2 ± 7.5 |
| Body weight | kg | 63.3 ± 10.9 (40-98) | 62.3 ± 12.0 | 62.3 ± 12.0 |
| Body mass index | kg/m² | 25.3 ± 3.0 | 25.3 ± 3.0 |
| ALT | U/L | 85.3 ± 64.5 | 85.3 ± 64.5 |
| HCV RNA titer | IU/mL | 1927 ± 1415 | 1927 ± 1415 |
| Previous treatment | Naïve/Retreatment | 97/45 | 97/45 |
| Fibrosis | F0/F1/F2/F3/F4 | 4/30/28/21/5 | 4/30/28/21/5 |
| Activity | A0/A1/A2/A3 | 0/32/54/2 | 0/32/54/2 |

ALT: alanine aminotransferase; HCV: hepatitis C virus.

### Table 2: Comparison of the clinical characteristics between responders and null responders

| Characteristics | Responders | Null responders | P |
|-----------------|------------|----------------|---|
| Number of patients | 142 | 17 | NS |
| Gender | Male; Female | 70; 53 | 10.7 | NS |
| Mean age (range) | Years | 56.3 ± 10.2 | 57.2 ± 7.5 | NS |
| Body weight | kg | 62.3 ± 12.0 | 62.3 ± 12.0 | NS |
| Body mass index | kg/m² | 25.3 ± 3.0 | 25.3 ± 3.0 | NS |
| ALT | U/L | 85.3 ± 64.5 | 85.3 ± 64.5 | NS |
| HCV RNA titer | IU/mL | 1927 ± 1415 | 1927 ± 1415 | NS |
| Previous treatment | Naïve/Retreatment | 97/45 | 97/45 | NS |

ALT: alanine aminotransferase; HCV: hepatitis C virus.

**DISCUSSION**

The guidelines in Japan for the treatment of patients with chronic hepatitis C recommend that Peg–IFNα2b/ribavirin treatment is continued for 72 wk in patients who have remained positive for HCV RNA after 12 wk of treatment, but who become negative for HCV RNA after 13-36 wk of treatment is continued for 72 wk in patients who have remained positive for HCV RNA after 12 wk of treatment, and 45 patients had received previous treatment. Eighty-eight patients underwent a liver biopsy. Inflammatory activity was classified as A0: 0; A1:32; A2: 54; and A3: 2 patients, and the fibrosis score was F0: 4; F1: 30; F2: 28; F3: 21; and F4: 5 patients, respectively. At the end of the study (72 wk), the overall SVR rate of all patients was 60/142 (42.3%), that of responders was 60/125 (48.0%) and that of null responders was 0/17 (0.0%).

Factors associated with a null response

There were 17 patients (12.0%) who were null-responders at 36 wk. A comparison of the clinical characteristics between the responders and null-responders is shown in Table 2. There were no significant differences between responders and null-responders with regard to gender, age, body weight, body mass index, previous treatment with IFN, baseline HCV RNA levels, serum ALT levels, or stage of fibrosis (Table 2). However, the HCV RNA levels at 1 wk and 4 wk after initiating treatment were significantly higher in null-responders compared with responders. Furthermore, the decrease rates of HCV RNA after 1 and 4 wk of treatment were significantly worse for null responders than for the responders. These results seem to be reasonable, because null responders had little or no decrease in their HCV RNA titer. The probability of SVR is also dependent on the speed of the decline in the viral load. A faster HCV RNA decline to an undetectable level means longer duration viral suppression, which can be translated to a higher chance of SVR. A large combined dataset including 569 genotype 1 HCV infected patients treated by Peg–IFNα2b/ribavirin therapy, further studies are needed to confirm our findings and to identify other useful predictive factors.

In the present study, the null response was not associated with gender, age, or previous IFN therapy. With
null responders to Peg-IFNα-2b/ribavirin therapy

regard to gender, it has been reported that male patients have a higher tendency to achieve SVR than female patients\(^1\). However, this was not shown to be the case in our study of null-responders. Regarding age, there have been reports suggesting that there is a relationship between patient age and SVR\(^2,3\). Although the SVR rate is reported to be lower in elderly patients than in younger patients\(^4\), there were no differences in age between null-responders and responders in this study. In our study, previous IFN therapy did not affect the null-response. The reasons for the equivalent response rates in subjects with a prior IFN history are unclear. Further validation using larger-scale studies is required to clarify the significance of these factors in null responders.

There are many predictive factors for SVR in Peg-IFN/ribavirin therapy. The virus itself is one factor, and it has been reported that amino acid substitutions in the core region are regarded as predictors of the response to Peg-IFN/ribavirin therapy in Japanese patients infected with HCV genotype Ib\(^5,6\). The substitution of amino acid (aa) 70 and 91 in the core region can predict the response to Peg-IFN/ribavirin combination therapy\(^7,8\). Mutations in the interferon sensitivity determining region (ISDR) are also associated with the response to combination therapy with Peg-IFN/ribavirin\(^9\). It has been reported that amino acid substitutions in the core and mutations in the ISDR are predictive of virological response to combination therapy in patients with HCV genotype Ib and a high viral load\(^10\). On the other hand, single nucleotide polymorphisms (SNPs) near the IL28B gene on chromosome 19 in the host have been suggested to be strongly associated with a null virological response\(^11-13\). Host genetics also may be useful for predicting the drug response.

In conclusion, the HCV RNA titer after 1 wk and 4 wk of treatment may be a useful predictive factor for null-responders to Peg-IFNα-2b/ribavirin therapy. However, further investigation is needed to determine the optimal time when Peg-IFNα-2b/ribavirin therapy should be discontinued for null-responders.

**Applications**

It would be useful to predict null responders earlier in the course of the disease in order to both avoid adverse effects and to achieve better disease control. However, further investigation is needed to determine the optimal time to determine whether to discontinue the Peg-IFN/ribavirin therapy for null-responders.

**Peer reviews**

Hepatitis C continues to be an important public health issue worldwide. How to deliver individualized therapy with interferon and ribavirin is a significant challenge. Therefore, the authors evaluated clinical and virological parameters before and after therapy in 142 patients with HCV genotype Ib. The conclusion was that higher HCV loads at week 1 and 4 after therapy can predict null response. This is an interesting report of clinical characteristics of null responders to Peg-IFN/ribavirin therapy for chronic hepatitis C. It is of clinical significance.

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