Four-week pegylated interferon α-2a monotherapy for chronic hepatitis C with genotype 2 and low viral load: A pilot, randomized study

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AIM: To assess the efficacy and advantages of 4-wk pegylated interferon α-2a (peg-IFN-α2a) monotherapy for chronic hepatitis C patients with strong predictors of sustained virologic response (SVR).

METHODS: Patients (n = 33) with genotype 2 and low viral load (< 100 KIU/mL), who became HCV RNA negative after 1 wk of IFN treatment, were randomly allocated to receive a 4- or 12-wk treatment course at a ratio of 2:1, respectively, with a subsequent 24-wk follow-up period. Peg-IFN-α2a was administrated subcutaneously at a dose of 180 µg or 90 µg once weekly. SVR was defined as absence of serum HCV RNA at the end of follow-up period.

RESULTS: All patients completed the treatment schedule, and more than half were symptom-free during the treatment. In the 4-wk treatment group, 20 of 22 (91%) patients achieved SVR. Two patients relapsed, but achieved SVR following re-treatment with peg-IFN-α2a alone. In the 12-wk treatment group, 11 of 11 (100%) patients attained SVR.

CONCLUSION: Our results show that a 4-wk course of peg-IFN-α2a monotherapy can achieve a high SVR rate in “IFN-sensitive” patients, without negatively affecting outcome.

Key words: Chronic hepatitis C; Pegylated interferon alpha-2a monotherapy; Genotype 2; Low viral load; Randomized pilot study

INTRODUCTION

Pegylated interferon alpha (peg-IFN-α) in combination with ribavirin for 24 wk is currently recommended as a standard treatment for patients with hepatitis C virus (HCV) genotypes 2 and 3, because prolongation of treatment duration to 48 wk does not always provide a substantial gain in the sustained virologic response (SVR) rate[5]. In contrast, short-term combination treatment (i.e. less than 24 wk of duration) has been evaluated in genotype 2 and 3 patients with or without initial virological response[6-11]. Shorter treatment may lead to a substantial reduction in patients’ burden and to the avoidance of premature termination of treatment without adversely affecting the outcome. Still, the pros and cons of a shorter treatment have not been conclusively defined and treating patients for less than 24 wk is still controversial.

A recent trend in the treatment strategy for chronic hepatitis C is the development of tailored or
individualized treatment regimens based on major strong predictors of SVR to IFN-based treatment, such as HCV genotype [23,12-17], pretreatment viral load [24,12,14,18], and initial virologic response to treatment [13,10-24]. Further subdivision or stratification of patients by combining these predictors may allow the development of more rational and optimal regimen without adversely affecting the outcome: e.g., treatment duration or combination with or without ribavirin. Specifically, a subgroup of genotype 2 patients with low viral load showed an excellent response even to conventional IFN monotherapy [12,14,18]. Furthermore, if initial virologic response is also taken into consideration in determining treatment regimen for the “IFN-sensitive” patient subgroup, even a shorter course of peg-IFN-α-2a monotherapy might result in a high SVR rate without adversely affecting the outcome.

In the present study, we evaluated the efficacy and tolerability of a 4-wk peg-IFN-α-2a monotherapy for “IFN-sensitive” patients with genotype 2 and low viral load, who became HCV RNA negative after 1 wk of treatment, in a pilot, randomized trial comparing a 4-wk versus a 12-wk treatment schedule. This study may allow us to substantially reduce the total dose and duration of peg-IFN-α treatment and to spare the use of ribavirin in the “IFN-sensitive” patient subgroup.

**MATERIALS AND METHODS**

**Study population**

Thirty-seven patients chronically infected with HCV genotype 2 and low viral load were consecutively enrolled in this pilot randomized study. They received short-term peg-IFN-α-2a monotherapy at the Department of Gastroenterology and Hepatology, Kashiwa Hospital, the Jikei University School of Medicine, between August 2006 and July 2007. Eligible patients had anti-HCV antibodies, infection with HCV genotype 2 confirmed by polymerase chain reaction (PCR)-based method [25], serum HCV RNA levels < 100 kilo-international units (KIU)/mL by a quantitative PCR assay (Amplicor HCV version 2.0, Roche Diagnostics) with a lower detection limit of 50 IU/mL. Peg-IFN-α-2a (Roche, Nutley, NJ) at a dose of 180 µg (platelet count > 90 × 10⁹/µL and neutrophil count > 1500/µL) or 90 µg (< 90 × 10⁹/µL and < 1500/µL, respectively) was administered subcutaneously once weekly. During the treatment, the dose of peg-IFN was adjusted based on platelet and/or neutrophil counts determined before each administration: Peg-IFN was reduced from 180 to 90 µg when platelet or neutrophil counts fell below 90 × 10⁹/µL and 1500/µL, respectively, and from 90 to 45 or 30 µg when platelet or neutrophil counts fell below 70% of the values observed the previous week. Peg-IFN was discontinued when the platelet count, the neutrophil count, or the hemoglobin value dropped below 25 × 10⁹/µL, 500/µL, and 8.5 g/dL, respectively.

Clinical, laboratory and hematological data were assessed once weekly during the treatment and every 4 wk during the 24-wk follow-up period. Virologic assessment was performed after 1 wk from the initiation of treatment, at the end of treatment, and every 4 wk during the follow-up period. Sustained virologic response (SVR) was defined as undetectable serum HCV RNA, using a qualitative PCR assay (Amplicor HCV version 2.0, Roche Diagnostics) at the end of follow-up period. Safety was monitored clinically by careful interview and medical examination throughout the study.

**Statistical analysis**

The χ² test, Fisher’s exact two-tail test, or Mann-Whitney test were used for statistical comparisons between groups, where appropriate. Treatment outcomes were analyzed on an intention-to-treat basis. All P values for statistical tests were two-tailed and values less than 0.05 were considered statistically significant. All calculations were performed using the SPSS 15.0 statistical package (SPSS, Chicago, IL).

**RESULTS**

**Patient characteristics**

Of 37 patients, 33 (89%) showed VR after 1 wk
of treatment. The 33 patients were subsequently randomized to the 4-wk (n = 22) or the 12-wk (n = 11) treatment arms (Table 1, Figure 1). There was no statistically significant difference between the two groups as far as the baseline characteristics features were concerned. Irrespective of the treatment course, all 33 patients completed the treatment and were closely followed up as scheduled. None of the patients was lost to follow-up. None of the patients received growth factors for cytopenias, such as granulocyte-colony stimulating factor and erythropoietin. A liver biopsy was not available in 3 patients because of a bleeding disorder (n = 1, 4-wk treatment group) or because of patients’ refusal (n = 2, both for the 4-wk treatment group).

**Sustained virological response rates**

In the 4-wk treatment group, 20 of 22 (91%) patients achieved SVR. Two patients relapsed 8 wk after the end of treatment. In the 12-wk treatment group, 11 of 11 (100%) patients attained SVR. No statistical difference was observed between both groups as to the SVR rates. The two patients who relapsed were offered re-treatment (4-wk and 12-wk regimens, respectively): both agreed and achieved SVR.

**Predictors of sustained virological response or relapse**

Univariate analyses failed to identify factors (including patients’ age, body weight, and the presence of steatosis) associated with SVR or relapse.

**Safety**

Six patients in the 4-wk treatment group and five in the 12-wk treatment group complained of low-grade fever, headache, or malaise, but these symptoms were well tolerated during treatment. The dose of peg-IFN-α-2a was reduced in three (all for thrombocytopenia) and four (two for neutropenia and two for thrombocytopenia) patients, respectively. Consequently, the cumulative dose of peg-IFN-α-2a was 180 to 720 μg and 1350 to 2160 μg, respectively. All patients recovered completely from the adverse events after the completion of treatment.

**Medication price**

On the basis of current prices in Japan, the cost of medication (peg-IFN-α-2a of 90 or 180 μg weekly) for 4-wk treatment course is between 536 and 1044 USD, and that for 12-wk treatment course is between 1608 and 3131 USD.

**DISCUSSION**

The results of this randomized pilot study suggest that a subgroup of patients could achieve a sufficiently high rate of SVR after only a 4-wk course of peg-IFN-α-2a monotherapy. One of the most IFN-sensitive subgroups appears to include patients with genotype 2 and low viral load who exhibit VR after 1 wk of treatment. Patients with genotype 2 or 3 are more sensitive to peg-IFN-α plus ribavirin treatment than those with genotype 1, and the current recommendation advocates a 24-wk treatment course, because more than 80% of the former group will attain SVR [3,7,10,27]. Recently, several studies suggested that the treatment duration could be shortened from 24 to between 12 and 16 wk without adversely affecting outcome in patients with genotype 2 or 3 who achieve VR after 4 wk of treatment [8,9,11]. In contrast, large trials indicated that shortening the treatment duration to 16 or 14 wk lessened the SVR rates [9,10]. It remains controversial whether the optimal
treatment duration is 24 wk or less than 24 wk for patients with genotype 2 or 3. A shorter treatment may not to be suitable for every patient with genotype 2 or 3. There may be a need to investigate whether the 4 wk timepoint from the beginning of treatment is appropriate to predict the therapy outcome after 24-wk treatment course.

There is ample evidence that peg-IFN-α plus ribavirin treatment is more beneficial in patients with genotype 2 than those with genotype 3. This suggests that treatment regimens should be tailored or individualized for each genotype, with a special emphasis on the duration of treatment. As for patients with genotype 2 alone, even high-dose conventional IFN-α monotherapy for 24 wk produced an SVR rate of 78%.[14] Furthermore, the inclusion of baseline viral load and initial virologic response, as strong predictors of SVR independent of genotype,[4,7-10] may identify patients suitable for shorter treatment in a more accurate way. In a small size study, an SVR rate of 100% was reported in patients with genotype 2a and low viral load (<100 KIU/mL) treated with IFN-α for 6 wk.[28]

In another study, 89.5% and 100% of patients, without genotype 1 and high viral load (>100 KIU/mL), who showed VR after 2 wk of treatment, achieved SVR with 8-wk and 24-wk peg-IFN-α2a monotherapy, respectively.[29] Although the sample size was very small, this pilot randomized trial suggested that the duration of peg-IFN-α2a monotherapy may be further shortened while maintaining a high SVR rate by dividing patients according to the presence or absence of strong predictors of response.

Common or characteristic adverse events are more severe and frequent in the combination treatment with ribavirin than in IFN-α or peg-IFN-α monotherapy, especially with prolonged treatment duration, leading to frequent withdrawals from treatment, because ribavirin accumulates in various tissues as well as in erythrocytes.[23,24] Therefore, only a minority of patients in need of therapy actually receives peg-IFN-α plus ribavirin treatment. Before participation in this trial, IFN-based treatment has been withheld from some patients for a variety of reasons such as advanced age, or the relatively low hemoglobin level and/or platelet count. Symptoms recorded in this study were mild or few, supporting the view that a short treatment course is safer and associated with few adverse events and less frequent withdrawal from treatment.[1,2,3,4,12,13] Our trial demonstrated that a 4-wk peg-IFN-α2a monotherapy was safe for such patients, and suggested that the indication for treatment could be extended to include patients considered otherwise unsuitable for the peg-IFN-α plus ribavirin combination therapy.

The combination treatment is costly, and the longer the treatment duration, the higher the cost of treatment. Currently, the cost of treatment of a person weighing 65 kg who receives peg-IFN-α2a at 180 µg weekly and ribavirin at 800 mg daily for 24 wk is approximately 11,253 USD in Japan. Thus, a 4-wk peg-IFN-α2a monotherapy would achieve a >90% reduction in cost and drug exposure. When one adds the costs of medical consultation and laboratory tests, the 4-wk peg-IFN-α2a monotherapy provides a substantial saving in costs and inconvenience compared to the extended treatment.

In conclusion, the present study showed high SVR rates in genotype 2 patients with low viral load who had undetectable serum HCV RNA after 1 wk of treatment, treated with a 4-wk course of peg-IFN-α2a monotherapy. Tailoring or individualizing treatment to individual patients would considerably reduce both patients’ and society burdens, without adversely affecting the clinical outcome.

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