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Early dynamics of viremia in patients with genotype 1b chronic hepatitis C: Peg-IFNα2a shows earlier viral decline than peg-IFNα2b in combination therapy with ribavirin

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background: We aimed to assess differences in early viral dynamics following treatment with either peg-IFNα2a or peg-IFNα2b in combination with ribavirin in patients with chronic genotype 1b HCV infection.

Material/Methods: Sixty-one patients in the peg-IFNα2a + ribavirin treatment (group α2a) and 88 patients in the peg-IFNα2b + ribavirin treatment (group α2b) were retrospectively analyzed. The early dynamics of HCV RNA over 12 weeks were evaluated. Sustained virological response (SVR) was defined as undetectable HCV RNA at week 24 after end of therapy. First- (day 0–1) and second-phase (day 1–28) viral decline rates were calculated in accordance with theoretical formulae.

Results: Baseline HCV RNA concentrations were almost similar between the 2 groups. In group α2a, viral decline was significantly greater than in group α2b at weeks 4, 8, and 12. In group α2a, viral decline was significantly greater in SVR patients than in non-SVR patients at week 2, whereas significantly greater viral decline in SVR patients was found during weeks 1–12 in group α2b. The first-phase viral decline rate was significantly larger in group α2a than in group α2b (1.31±0.84 *vs.* 0.70±0.97 log IU/mL/day; p<0.0001). Within SVR patients, first-phase viral decline rate was significantly larger in group α2a compared with group α2b (1.45±0.85 *vs.* 0.78±1.0 log IU/mL/day; p<0.0001). Second-phase viral decline rate was comparable between the groups.

Conclusions: Peg-IFNα2a showed earlier viral decline than peg-IFNα2b and the difference was obvious, especially in the first-phase viral decline.

key words: **chronic hepatitis C • HCV • peg-interferon • viral kinetics**

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Background

Approximately 170 million people are infected with hepatitis C virus (HCV) worldwide and natural history studies show that 5–20% of patients develop cirrhosis after approximately 20 years of infection [1]. Currently, the pegylated-interferon (peg-IFN) plus ribavirin combination therapy has become the standard of care for chronic HCV-related liver disease because it achieves the highest rates of sustained virological response (SVR), defined as undetectable HCV RNA in blood 24 weeks after completion of therapy [2]. Moreover, peg-IFN and ribavirin are effective in treating chronic hepatitis C in children [3]. However, in patients infected with genotype 1 or 4 HCV, only about half achieve SVR following combination therapy, and genotype 1b in high viral loads accounts for >70% of patients with HCV infection in Japan [4]. The response to IFN is influenced by viral factors including viral load and genotypes, and host factors such as sex, age, insulin resistance, staging of the disease, and responses to previous antiviral therapies, as well as therapeutic factors such as dose and duration of treatment [5–8].

The stability of HCV RNA levels in individual patients with chronic HCV infection represents a steady state in which viral production is equivalent to viral elimination [9]. Initial viral dynamic studies of HCV showed the standard biphasic decline model after initiation of unmodified IFNα [9–11]. Peg-IFN + ribavirin therapy produced a biphasic viral decline, as was illustrated in initial studies. The first-phase decline in viral loads was rapid, usually occurring within the first 24 h, and was followed by a second, slower phase. The first-phase decline was dose-dependent and the second-phase decline, which was predictive of an SVR, showed considerable variability among individual patients [12,13]. Recently, mathematical modeling approaches have been developed to interpret the complex HCV kinetics observed in patients treated with peg-IFN and ribavirin [14–17]. The studies of viral kinetics in chronic hepatitis C patients during antiviral therapies have been described and early monitoring of viral decline was used to predict treatment outcomes [18–21].

In the IDEAL trial, antiviral efficacy was compared between peg-IFNα2a and peg-IFNα2b in combination therapy with ribavirin for patients with HCV genotype 1 infection, and the SVR rates, as well as the adverse effects, did not differ between the 2 groups in their standard dosing regimens [22–24]. However, there is limited information on the difference of viral kinetics, especially in the early-phase viral decline, between peg-IFNα2a and peg-IFNα2b in combination therapy with ribavirin for chronic hepatitis C. In the present study, the early dynamics of serum HCV RNA and the rate of viral decline were retrospectively analyzed in Japanese patients with genotype 1b chronic hepatitis C with high viral loads who received treatment with peg-IFNα2a + ribavirin or peg-IFNα2b + ribavirin.

Material and Methods

Patients with chronic hepatitis C who were treated with peg-IFN + ribavirin combination therapy in the National Hospital Organization Group of Japan between 2007 and 2009 were enrolled for this study and retrospectively analyzed. The study protocol was approved by the Ethics Committee of the National Hospital Organization, and written informed consent was obtained from all patients. According to the standard protocols in Japan, patients received subcutaneous injection of peg-IFNα2a (180 μg) or peg-IFNα2b (1.5 μg/kg) once weekly for 48 or 72 weeks. Ribavirin (15 mg/kg/day) was included in both protocols. Doses of peg-IFN and ribavirin were reduced in some patients because of anemia, leukocytopenia, thrombocytopenia, or other adverse events, but not within the first 4 weeks. Serum HCV RNA concentrations were determined by COBAS TaqMan PCR HCV test (Roche Diagnostics, Tokyo, Japan) at baseline and at weeks 1, 2, 4, 8, and 12 after treatment initiation. SVR was defined as undetectable HCV RNA at week 24 after completion of therapy. The first-phase (24-h virological response) and second-phase (day 1–28) viral decline rates by treatment were calculated as shown in Figure 1. The calculation is based on a biphasic viral decline model where the first-phase is the sharp decline observed over the first 24 h of treatment and the dull decline of the second-phase continues for the following 27 days [25–27]. This calculation method was first introduced in the International Liver Congress 2009, 44th Annual Meeting of the European Association for the Study of the Liver [28].

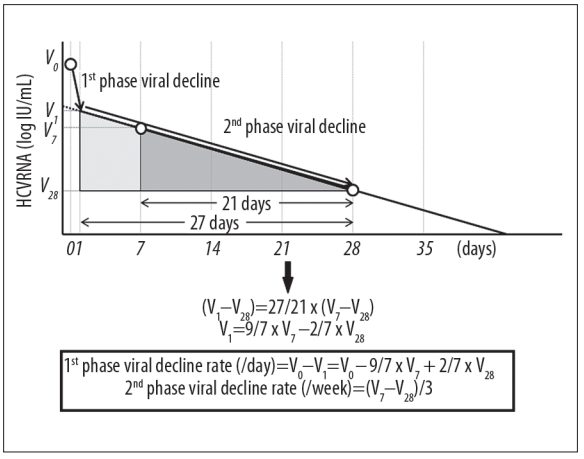

Figure 1. Early viral kinetic model during peg-IFN plus ribavirin combination therapy. The first-phase decline slope for 24h should be sharp whereas the subsequent second-phase decline slope should be dull. Expected first-phase and second-phase viral decline rates were calculated from the formulae presented under the graph.

Results are expressed as means ±standard deviation. Differences between categorical variables were analyzed by Fisher's exact test or chi-square test. Mann-Whitney *U* test was used for continuous variables. *P*-values <0.05 were considered statistically significant.

Results

A total of 149 patients were retrospectively analyzed; their baseline characteristics are shown in Table 1. All patients were infected with genotype 1b HCV with high viral loads; their baseline HCV RNA levels in serum were ⩾5.0 log IU/mL. The patients were divided into 2 groups: group α2a included 61 patients with peg-IFNα2a + ribavirin treatment and group α2b included 88 patients with peg-IFNα2b + ribavirin treatment (Table 1). Baseline serum HCV RNA concentrations were similar between the 2 groups (6.1±0.5

Table 1. Patient characteristics.

	Group α2a	Group α2b	P value
Number	61	88	
% of retreatment cases	41.0%	25.0%	NS
Gender (male/female)	30/31	42/46	NS
Age (years)	58.3±8.7	57.6±10.5	NS
Body mass index (kg/m^2)	22.4±2.1	23.5±2.5	NS
HCV RNA (log IU/mL)	6.1±0.5	6.2±0.6	NS
AST (IU/L)	51.0±26.5	55.5±40.3	NS
ALT (IU/L)	64.8±40.7	69.8±66.8	NS
GGT (IU/L)	54.4±64.2	52.2±54.8	NS
Hemoglobin (g/dL)	14.0±1.4	13.8±1.4	NS
White blood cell (/μL)	5.008±1.320	5.002±1.374	NS
Platelet (×10^4/μL)	16.1±4.7	19.1±9.0	NS

AST – aspartate aminotransferase; ALT – alanine aminotransferase; GGT – γ-glutamyl transpeptidase; NS – not significant.

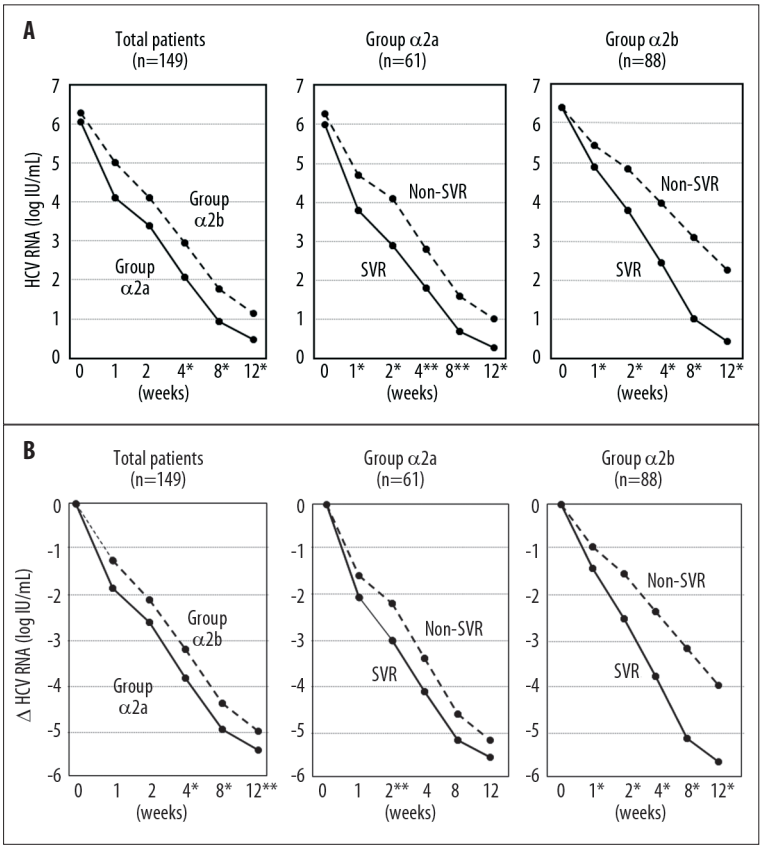

Figure 2. (**A**) Serum HCV RNA values in patients with chronic hepatitis C during peg-IFN plus ribavirin combination therapy. The levels were compared between group α2a and group α2b (left panel), between SVR and non-SVR patients in group α2a (center panel), and between SVR and non-SVR patients in group α2b (right panel). * p<0.01, ** p<0.05. (**B**) Levels of viral decline (HCV RNA) from baseline in patients with chronic hepatitis C during peg-IFN plus ribavirin combination therapy. Levels were compared between group α2a and group α2b (left panel), between SVR and non-SVR patients in group α2a (center panel), and between SVR and non-SVR patients in group α2b (right panel). * p<0.01, ** p<0.05.

vs. 6.2±0.6 log IU/mL, respectively). SVR rate was lower in group α2a (54.1%) than in group α2b (61.4%), although the difference was not statistically significant (data not shown).

HCV RNA concentrations declined earlier in group α2a, and group α2a showed significantly lower concentrations than group α2b at weeks 4, 8, and 12 after starting treatment (Figure 2A). In both groups, HCV RNA levels were significantly lower at weeks 1, 2, 4, 8, and 12 in SVR patients compared with non-SVR patients (Figure 2A). The level of viral decline to baseline levels (net viral decline) was significantly greater at weeks 4, 8, and 12 in group α2a than in group α2b (Figure 2B). The level of viral decline in SVR patients was significantly greater than that in non-SVR patients at

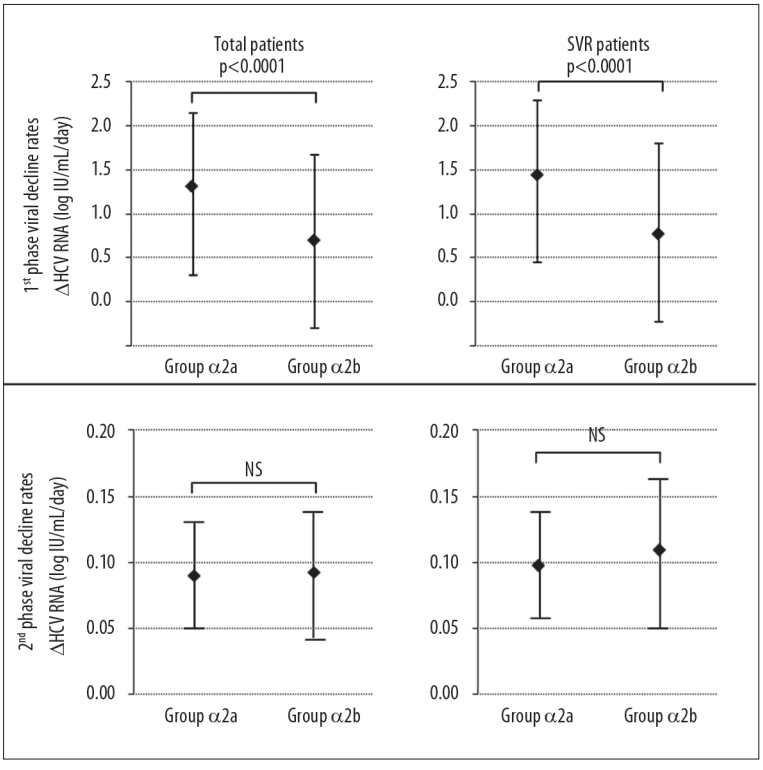

Figure 3. Comparison of first- and second-phase decline rates between group α2a and group α2b in total patients (left panels) and in SVR patients (right panels). Diamonds with lines indicate means ± standard deviation.

week 2 in group α2a, whereas this was evident at all assessment time-points in group α2b (Figures 2B).

In both the total population and SVR patients, first-phase viral decline rates were significantly higher in group α2a compared with group α2b (1.31±0.84 *vs.* 0.70±0.97 log IU/mL/day in total population, p<0.0001; 1.45±0.85 *vs.* 0.78±1.0 log IU/mL/day in SVR patients, p<0.0001) (Figure 3, upper panels). On the other hand, second-phase viral decline rates were similar in the 2 groups (Figure 3, lower panels).

Discussion

As shown in Table 1, no significant differences were found in sex, age, viral load, body weight, platelet counts, or biochemical analysis that would influence the response to antiviral treatments. Retreatment patients were included in this study; their percentage was higher in group α2a than in group α2b (41.0% *vs.* 25.0%), but the difference was not significant. Of note, previous treatments in all retreatment patients were unmodified IFN monotherapy, which is generally ineffective for patients with genotype 1 HCV (SVR rate <5%). Therefore, "retreatment patient" does not mean lower responder to peg-IFN + ribavirin combination therapy and all patients enrolled in this study were naïve for the combination therapy. In patients who had experienced liver biopsies (group α2a, 57 cases; group α2b, 60 cases) there were no significant intergroup differences in histopathological staging and grading (data not shown). Dose reduction of peg-IFNα and/or ribavirin, which weakens the antiviral effect, was not considered in this study, and the duration of treatment was not fixed (48 or 72 weeks). Therefore the final outcome of the treatments, SVR rates, cannot be fairly compared between the groups. However, early viral kinetics, especially the viral decline rate, may be worth evaluating because no dose reduction was done within the first 4 weeks.

Viral decline was significantly greater in group α2a compared with group α2b during the 4-12 weeks after treatment initiation (Figures 2, 3), suggesting that early viral response to peg-IFNα2a may be better than that to peg-IFNα2b. In group α2b, non-SVR patients had significantly limited viral decline during weeks 1–12 compared with SVR patients, whereas limited viral decline in non-SVR patients was found only at week 2 in group α2a (Figure 3). Accordingly, viral decline may be useful to predict SVR in group α2b but not in group α2a.

As pharmacokinetic parameters, first- and second-phase viral decline rates were compared between group α2a and group α2b. Based on the model of HCV kinetics [25,26], we devised formulae for calculating first- and second-phase viral decline rates using serum HCV RNA concentrations at baseline and week 1 and 4 after treatment initiation (Figure 1). As a result, the first-phase viral decline rate was significantly greater in group α2a, whereas the second-phase viral decline rate was comparable between the 2 groups. In some studies, ribavirin did not appear to affect first-phase viral decline, and increased second-phase viral decline when IFN response was low [27,29–32]. It has been suggested that first-phase decline reflects a dose-effect and the pharmacokinetic properties of peg-IFNs, and that the slope of the second-phase decline reflects inter-patient variability [9,33]. Peg-IFNα2a and peg-IFNα2b have different pharmacokinetics; their half-lives in plasma are approximately 77 and 40 h, respectively [34,35]. Therefore, among therapeutic factors, administered dose and half-life may be the main factors affecting the difference in first-phase viral decline rate between treatments with peg-IFNα2a *vs.* peg-IFNα2b.

In practice, it is difficult to fairly evaluate the effect of different antiviral protocols, because virological and host factors that also affect outcomes are complex. For example, novel factors such as substitution of amino acids 70 and 91 in the core region of HCV-1b [36] and genetic variation in IL28B [37–39] are associated with outcomes of antiviral therapy. In future, if these factors can be evaluated more simply and easily, more successful therapeutic protocols may be selected for individual patients as tailor-made therapy.

Conclusions

In our study population, peg-IFNα2a showed earlier viral decline than peg-IFNα2b, and the difference was particularly obvious in the first-phase viral decline, although no significant difference was shown in SVR rate between the treatments.

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