Extending Combination Therapy with Peginterferon plus Ribavirin for Genotype 2 Chronic Hepatitis C Virological Responders: A Pilot Study of 7 Cases

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\textbf{Key Words}
Hepatitis C virus \cdot Genotype 2 \cdot Interferon \cdot Ribavirin \cdot Combination therapy, extended \cdot Early virological response

\textbf{Abstract}

\textbf{Objective:} In treatment-resistant patients with genotype 2 chronic hepatitis C the suitable treatment duration is still unclear. The aims were to investigate extending combination therapy with peginterferon plus ribavirin for genotype 2.

\textbf{Methods:} 7 patients infected with genotype 2 at a high viral load and who did not achieve a sustained virological response (SVR) with the first course of 24-week IFN plus ribavirin were recruited into the study protocol with a total of 48 weeks of peginterferon plus ribavirin therapy.

\textbf{Results:} SVR was achieved in 5 of 7 patients (71%). All 4 patients (100%) who were in relapse with the first course achieved SVR. Only 1 of 3 patients (33%) who had a non-virological response (NVR) with the first course achieved SVR. All 4 patients who had an early virological response (EVR) with the first course achieved EVR and SVR. Two of 3 patients who had no EVR with the first course also did not achieve EVR and SVR. One patient who had no EVR or a NVR during the first course achieved EVR and SVR with the second course.

\textbf{Conclusions:} Our results suggest that extending combination therapy for genotype 2 chronic hepatitis C might be useful for patients who relapse following 24-week combination therapy.
especially in genotype 2 infection, it is necessary to identify those patients who could achieve SVR with a shorter treatment course (16 weeks or less) to free them of unnecessary side effects and reduce costs, preferably as early as possible [6–8]. However, we also sometimes encounter treatment-resistant patients infected with genotype 2 [3, 10, 11]. Our recent report based on 24-week combination therapy showed that 17.5% of patients infected with genotype 2a were not able to achieve SVR, and especially that 81.5 and 18.5% of the non-SVR patients were in relapse or had a non-viral response (NVR), respectively [11]. Thus, the suitable treatment duration, based on the consideration of risk/benefit and cost/benefit, is still unclear in patients infected with genotype 2.

The present study included 7 Japanese adults with genotype 2 and a high viral load, who received a second course of combination therapy. The aims of the study were to investigate extending combination therapy with peginterferon (PEG)-α-2b plus ribavirin for genotype 2 chronic hepatitis C.

Materials and Methods

Study Population

A total of 292 HCV genotype 2-infected Japanese adult patients were consecutively recruited into the study protocol of the combination therapy with IFN (PEG-IFNα-2b or IFNα-2b) plus ribavirin for 24 weeks between March 2002 and September 2008 at Toranomon Hospital, Tokyo, Japan. Among these, 7 of 52 patients who were not able to achieve a sustained virological response were recruited into the study protocol of 48-week combination therapy with PEG-IFNα-2b plus ribavirin. They fulfilled the following inclusion criteria: (1) no SVR with the first course of combination therapy regardless of completing the 24-week therapy; (2) combination therapy was stopped before completing the 24-week therapy due to a decrease in HCV RNA of <2.0 log at 12 weeks after starting treatment based on qualitative PCR analysis [12, 13]; (3) negative for hepatitis B surface antigen (radioimmunoassay, Dainabot, Tokyo, Japan), positive for anti-HCV (third-generation enzyme immunoassay, Chiron Corp, Emeryville, Calif., USA), and positive for HCV RNA qualitative analysis with PCR (Amplicor, Roche Diagnostic Systems, Pleasanton, Calif., USA); (4) infected with HCV genotype 2a or 2b alone; (5) high viral load (>100 KIU/ml) by quantitative analysis of HCV RNA with PCR (Amplicor GT HCV Monitor v2.0 using the 10-fold dilution method, Roche Molecular Systems Inc.) at least once every month before, during, and after therapy. The dynamic range of the assay was 5–5,000 KIU/ml. Samples collected during and after therapy that showed undetectable levels of HCV-RNA (<5 KIU/ml) were also checked by qualitative PCR (Amplicor HCV v2.0, Roche Molecular Systems Inc.), which has a higher sensitivity than quantitative analysis, and the results are expressed as positive or negative. The lower limit of the assay was 50 IU/ml.

Histopathological Examination of Liver Biopsies

Liver biopsy specimens were obtained percutaneously or at peritoneoscopy using a modified Vim Silverman needle with an internal diameter of 2 mm (Tohoku University style, Kakinuma Factory, Tokyo, Japan), fixed in 10% formalin, and stained with hematoxylin and eosin, Masson’s trichrome, silver impregnation, and periodic acid–Schiff after diastase digestion. All specimens for examinations contained 6 or more portal areas. Histopathological diagnosis was confirmed by an experienced liver pathologist (H.K.) who was blinded to the clinical data. Chronic hepatitis was diagnosed based on histological assessment according to the scoring system of Desmet et al. [15].

Results

Table 1 summarizes the characteristics of the 7 patients at commencement of the second-course combination therapy with PEG–IFN plus ribavirin. There were 5 men and 2 women, aged 40–65 (median 55) years. Two cases were genotype 2a, and the other 5 cases were genotype 2b. They received PEG–IFNα–2b at a median dose of 1.4 (range 1.1–1.7) µg/kg subcutaneously each week. They also received oral ribavirin at a median dose of 10.6

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Intervirology 2010;53:188–192
In patients infected with genotype 1, previous studies have demonstrated that SVR rates of late virological responders (HCV-RNA-positive at 12 weeks and negative 24 weeks after the start of treatment) could be improved when treatment was extended to 72 weeks, compared with a standard treatment duration of 48 weeks, largely as a result of reducing post-treatment relapse rates [16–20]. Thus, prolongation of therapy in genotype 1 may improve the virological response rate. However, it is not clear at present whether prolongation of treatment improves the SVR rate of treatment-resistant Japanese patients infected with genotype 2. This study of patients infected with genotype 2 showed that SVR rates of patients who were EVR and relapsed following the first course with a standard treatment duration of 24 weeks could be improved when treatment was extended to 48 weeks. Interestingly, 1 patient (case 5) who did not have EVR or NVR with the first course achieved EVR and SVR with the second course. This indicates that the SVR rates of patients who had an EVR with the second course might improve further by extending combination therapy regardless of NVR with the first course. To our knowledge, this is the first report to indicate that extending combination therapy to 48 weeks for genotype 2 might be useful.

In this study, 2 patients did not have an EVR or an NVR with both the first and second course and could not achieve SVR. The underlying mechanism(s) of the different virological responses to treatment in patients infected with genotype 2 is still unclear. Previous reports indicated that viral factors (e.g. viral load, aa substitutions in the NS5A region and core region, early viral kinetics, and periods from the start of treatment to initial point of undetectable HCV-RNA) and host factors (e.g. body mass index, fibrosis stage, and hepatocyte steatosis) might be important predictors of treatment response to IFN-related therapy in patients infected with HCV genotype 2a, in addition to treatment-related factors (e.g. treatment duration, and ribavirin dose) [6–11, 21–27]. One of the lim-
limitations to this study is that due to the small number of patients we were not able to investigate treatment-resistant factors. Further studies should be performed to identify these viral and host factors before the start of combination therapy. Furthermore, more effective therapeutic regimens, including triple therapy with PEG-IFN plus ribavirin and telaprevir, should be developed for these patients who could not achieve SVR by extending dual therapy of PEG-IFN plus ribavirin.

In conclusion, our results suggest that extending combination therapy to 48 weeks for genotype 2 chronic hepatitis C might be useful for patients who had a relapse following the first course of 24-week combination therapy. In the future a large-scale prospective study based on intention-to-treat analysis should be conducted to confirm the above findings.

Acknowledgement

This study was supported in part by a Grant-in-Aid from the Ministry of Health, Labor and Welfare, Japan.

References


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Intervirology 2010;53:188−192


