Outcome of Double-Filtration Plasmapheresis plus Interferon Treatment in Nonresponders to Pegylated Interferon plus Ribavirin Combination Therapy

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Key Words

Double-filtration plasmapheresis · Interferon- β · Peginterferon · Ribavirin · Sustained virological response · Relapse · Null virological response

Abstract

Objectives: We assessed the outcome of double-filtration plasmapheresis (DFPP) combined with pegylated interferon (PEG-IFN) and ribavirin (RBV) therapy in patients infected with hepatitis C virus (HCV)-1b whose HCV had not disappeared during PEG-IFN/RBV combination therapy, or who had relapsed after the end of the therapy. Additionally, we investigated factors predictive of sustained virological response (SVR), including host and viral genetic factors, to DFPP plus IFN/RBV therapy. **Methods:** A total of 40 patients infected with HCV-1b whose HCV virus had not been eradicated by previous PEG-IFN/RBV therapy were enrolled for treatment by DFPP plus IFN/RBV. Rapid virological response

(RVR) and SVR were assessed, and pretreatment factors associated with SVR – the interleukin (IL)28B gene, the IFN/RBV resistance-determining region (IRRDR) and the IFN sensitivity-determining region (ISDR) – were analyzed. **Results:** Of the 40 patients, 9 (23%) achieved RVR and 10 (25%) achieved SVR. The significant factors associated with SVR were IL28B major and RVR, as assessed by multivariate analysis ($p = 0.0182$, $p = 0.0005$). **Conclusion:** Patients whose HCV is not eradicated by previous PEG-IFN/RBV would be good candidates for combined DFPP and IFN/RBV retreatment provided they demonstrate IL28B major and have achieved RVR.

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Introduction

The most effective treatment for patients infected with genotype hepatitis C virus (HCV)-1b has been based on pegylated interferon plus ribavirin (PEG-IFN/RBV)

combination therapy since 2004 in Japan. Nonetheless, sustained virological response (SVR) rates for those infected with genotype HCV-1a and HCV-1b, the most common and the most difficult to treat, still hover around 50% [1, 2]. Moreover, retreatment with PEG-IFN/RBV of patients who resist initial PEG-IFN/RBV is frequently unsuccessful, with SVR rates of only 7–9% [3]. To enhance the SVR rate more effectively for these resistant cases, several approaches have been undertaken. One such therapy is double-filtration plasmapheresis (DFPP; approved in Japan in 2008 for the treatment of chronic hepatitis C (CHC) patients with genotype HCV-1b and high viral loads) in combination with IFN administration, which has produced a substantial reduction in the viral load during the early stages of treatment and has demonstrated a high SVR rate [4, 5].

Recent reports have revealed factors associated with response to PEG-IFN/RBV therapy in HCV-1b patients: single nucleotide polymorphisms, as host genetic factors, located in interleukin (IL)28B (rs8105790, rs11881222, rs8103142, rs28416813, rs4803219, rs8099917, rs7248668 and rs12979860) on chromosome 19 [6–9]; amino acid (aa) substitutions in nonstructural protein 5A (NS5A), especially those in the IFN/RBV resistance-determining region (IRRDR) [10], and the IFN sensitivity-determining region (ISDR) [11], as viral genetic polymorphisms.

In this study, we assessed the outcome of the use of DFPP combined with IFN therapy aimed at enhancing the efficacy of the treatment of CHC patients whose HCV had not disappeared by PEG-IFN/RBV combination therapy, or who had relapsed after the end of the therapy. Additionally, we investigated factors predictive of SVR, including host and viral genetic factors associated with response to DFPP plus IFN/RBV therapy.

Patients and Methods

Patients

A total of 40 patients whose HCV virus had not been eradicated by PEG-IFN α -2b plus RBV combination therapy received DFPP plus IFN treatment. The patients comprised 2 groups according to response to previous PEG-IFN/RBV treatment: continuous viremia throughout the observation period, referred to as the null virological response (NVR) group, and transient disappearance of serum HCV RNA at a certain point in time with a subsequent rebound in viremia either before or after the end of the treatment, referred to as the relapse group. All patients were confirmed positive for HCV RNA, had high levels of transaminase persisting for 6 months or longer, demonstrated genotype HCV-1b at levels exceeding 10^5 log IU/ml in blood (as determined before the start of therapy by real-time PCR), and were negative for hep-

atitis B surface antigen. Patients with platelet counts $\leq 10 \times 10^4/\mu\text{l}$, leukocyte counts $\leq 3,000/\mu\text{l}$ or hemoglobin levels ≤ 12 g/dl were excluded from the study. Informed written consent was obtained from each patient and the study protocol conformed to the ethical guidelines approved by the Ethics Committee of Kobe Asahi Hospital.

DFPP and Blood Collection

Blood collected from the peripheral vein for DFPP by a PlasmafloTM OP-18W filter (Asahi Kasei Medical, Tokyo, Japan) was separated into plasma and cell components. The virus was then removed from the plasma by a second filter (CascadefloTM EC-50W; Asahi Kasei Medical) of an average pore of 30 nm. For each session, the final volume of treated plasma was 50 ml/kg, the number of sessions was 5 over 2 weeks, and the intervals of administration of DFPP, based on the reduced plasma fibrinogen levels during DFPP, was decided by the physicians and as required by the patients.

Regimen of IFN with DFPP

During DFPP, the patients received different kinds of IFN: PEG-IFN α -2b plus RBV for 4 weeks; IFN- β 3 MU twice daily for 2 weeks and PEG-IFN α -2a plus RBV for 2 weeks; IFN- β 3 MU twice daily for 2 weeks and IFN- β 6 MU daily for 2 weeks; IFN- β 3 MU twice daily for 10 days, IFN- β 6 MU daily for 18 days and IFN- β 3 MU daily for 4 weeks; IFN- β 3 MU twice daily plus RBV for 4 weeks. The PEG-IFN dose was 1.5 μg of α -2b/kg and 180 μg of α -2a per week. After DFPP plus IFN treatment for 4 weeks, all the patients were scheduled to receive PEG-IFN/RBV combination therapy for 48 weeks. The RBV dose was 800 mg of α -2b/day and 600–800 mg of α -2a/day.

Laboratory Tests

HCV RNA was extracted from 140 μl of serum with the use of a commercially available kit (QIAmp viral RNA kit; Qiagen, Tokyo, Japan). The quantity of HCV RNA was converted to a log value at the beginning of the treatment (A) and at 4 weeks after the start of treatment (B). $\Delta\log$ was then calculated as follows: $\Delta\log = \log A - \log B = \log (A/B)$. Amplification of full-length NS5A and the core regions of the HCV genome was carried out as described [10]. Before the start of treatment, HCV aa substitutions were measured in NS5A, in IRRDR and in ISDR. Genetic polymorphism rs8099917 around the IL28B gene was determined by real-time PCR with the TaqMan assay. We defined the IL28B major allele as homozygous (TT) for the major sequence and the IL28B minor allele as homozygous (GG) or heterozygous (TG) for the minor sequence.

Statistical Analysis

Rapid virological response (RVR) was defined as undetectable serum HCV RNA at week 4. SVR was defined as undetectable serum HCV RNA by week 24 after treatment. RVR and a reduction in the HCV RNA viral load $\geq \log 2$ at week 4 after the start of treatment was assessed as being associated with SVR. The potential pretreatment factors associated with virological response including age, sex, body weight, the HCV RNA load, alanine aminotransferase (ALT), γ -glutamyl transpeptidase (γ -GTP), hemoglobin, platelets, total cholesterol, blood glucose level, single nucleotide polymorphisms in the IL-28B gene region, the mutation in NS5A, especially that in ISDR and IRRDR, were examined.

Table 1. Patient baseline characteristics

Age (years)	60.95±8.51
Sex (male/female)	13/27
Body weight (kg)	54.46±13.51
HCV RNA (KIU/ml)	6.06±0.90
Hemoglobin (g/dl)	12.18±2.94
ALT (IU/l)	37.15±30.73
γ-GTP (IU/l)	41.70±44.40
Platelets (×10 ⁴ /mm ³)	14.35±5.79
Blood glucose level	92.30±19.30
Total cholesterol (mg/dl)	151.03±32.54
IL-28 (major/minor)	18/40
ISDR	0.60±0.49
IRRDR	4.08±1.77

Data are shown as means ± SD.

Table 2. Rates of virological responses

Virological response	All	Previous relapse patients	Previous NVR patients	p value
RVR	9/40 (23)	8/18 (44)	1/22 (5)	0.0036
SVR	10/40 (25)	7/18 (39)	3/22 (14)	0.1401

Values in parentheses are percentages. Bold p values are significant.

Table 3. Association of baseline characteristics and clinical SVR and non-SVR

Factor	SVR (n = 10)	Non-SVR (n = 30)	p value
Age (years)	60.60±9.47	61.07±8.16	0.9626
Sex (male/female)	5/5	8/22	0.2464
Body weight (kg)	47.90±16.93	56.50±11.63	0.2717
Platelets (×10 ⁴ /mm ³)	17.76±6.26	13.21±5.14	0.0588
Hemoglobin (g/dl)	12.92±2.08	11.93±2.04	0.2540
γ-GTP (IU/l)	31.10±24.15	45.23±48.83	0.3814
ALT (IU/l)	45.60±41.18	34.33±25.73	0.4251
HCV RNA (KIU/ml)	5.97±1.00	6.09±0.87	0.4880
Blood glucose level	103.33±32.79	88.75±9.75	0.2216
T-Cho	155.20±29.69	149.63±33.32	0.5843
IL28B (major/minor)	8/2	10/20	0.0246
IRRDR mutations	3.60±0.92	4.23±1.94	0.4944
ISDR mutations	0.43±0.49	0.67±0.47	0.2850
Previous treatment response			
(Relapse/NVR)	7/3	11/19	0.1401
RVR/non-RVR	7/3	2/28	0.0002

Data are shown as means ± SD. Bold p values are significant.

Additionally, the significant factors associated with SVR were compared with those of NVR and relapse patients. Factors associated with the virological response were assessed by univariate analysis using the Mann-Whitney U test, Fisher's exact test or χ^2 test, and by multivariate analysis using logistic regression analysis. Variables with a p value <0.05 were considered statistically significant. All statistical analyses were carried out with EXCEL multivariate statistical analysis software version 6.0 (ESUMI Inc., Toyo, Japan).

Results

Treatment Responses and Viral Dynamics

The baseline characteristics of the patients and the laboratory data are shown in table 1. Of the 40 patients, 9 (23%) achieved RVR and 10 (25%) achieved SVR.

RVR was achieved in 44% (8/18) of previously relapsed patients and in 5% (1/22) of previously NVR patients, with a significant difference between the two groups (p = 0.0036; table 2). SVR was achieved in 39% (7/18) of relapsed patients and in 14% (3/22) of NVR patients, with no significant difference between the two groups (p = 0.1401; table 2). A reduction of ≥2 log in the viral load was observed in 61.5% (24/39). The number of patients who achieved ≥2 log reduction was larger in SVR than in non-SVR patients, with a significant difference between the two (p = 0.034).

Analysis of Factors Associated with SVR

By univariate analysis, the significant factors associated with SVR were IL28B major and RVR (p = 0.0246, p = 0.0002; table 3). By multivariate analysis, both factors were also significantly associated with SVR (p = 0.0182, p = 0.0005; table 4).

Analysis of the correlation between SVR and RVR in both groups revealed that of 18 previously relapsed patients, RVR was achieved in 100% (7/7) of the SVR patients, but in only 9% (1/11) of the non-SVR patients, with a significant difference between the two (p = 0.0011; table 5). Of 22 previously NVR patients, RVR was achieved in 0% (0/3) of the SVR patients and in 5% (1/19) of the non-SVR patients, with no significant difference between the two (p = 0.8636; table 6).

In previously relapsed patients, IL28B major was demonstrated in 86% (6/7) of the SVR patients and in 64% (7/11) of the non-SVR patients (p = 0.3235; table 5). In previously NVR patients, IL28B major was demonstrated in 67% (2/3) of the SVR patients, but in 16% (3/19) of the non-SVR patients; it was not associated with SVR in either relapsed or NVR patients (p = 0.1169; table 6).

Table 4. Factors associated with SVR by multivariate analysis

Factor	Odds ratio	95% CI	p value
Age (years)	0.994	0.914–1.080	0.8806
Sex (male/female)	2.75	0.626–12.085	0.1805
Body weight (kg)	0.953	0.896–1.014	0.1305
Platelets ($\times 10^4/\text{mm}^3$)	1.162	1.002–1.346	0.0464
Hemoglobin (g/dl)	1.264	0.880–1.814	0.2046
γ -GTP (IU/l)	0.99	0.967–1.014	0.4058
ALT (IU/l)	1.011	0.989–1.033	0.3330
HCV RNA (KIU/ml)	0.864	0.399–1.870	0.7110
Blood glucose level	1.041	0.987–1.098	0.1405
T-Chol	1.01	0.983–1.028	0.6404
IL28B (major/minor)	8	1.425–44.920	0.0182
IRRDR mutations	0.803	0.514–1.253	0.3328
ISDR mutations	0.375	0.063–2.244	0.2826
Previous treatment response			
(Relapse/NVR)	2.591	0.598–11.234	0.2034
RVR/non-RVR	32.667	4.548–234.616	0.0005

Bold p values are significant.

Discussion

SVR by PEG-IFN/RBV treatment of patients previously nonresponsive to PEG-IFN/RBV therapy is difficult to achieve. To enhance the SVR rate, several trials have been undertaken: among patients with relapse after previous treatment, those who attain SVR on retreatment require a longer period of therapy than that of the previous treatment [12]; retreatment of nonresponders with PEG-IFN- α 2b plus RBV therapy for 72 weeks increases SVR rates significantly compared with retreatment for 48 weeks [13].

An alternative therapeutic method is treatment with the use of DFPP, which was approved in Japan in 2008. Granulocyte apheresis, plasma exchange and hemofiltration are modalities that have shown a reduction of HCV RNA in blood during the treatment of HCV-infected patients for cryoglobulinemia and vasculitis [14, 15]. The mechanisms of plasmapheresis have been described as related to the enhancement of the effects of IFN therapy by synergistically removing HCV from the blood [16]. Hemodialysis, hemofiltration and peritoneal dialysis given to chronic dialysis patients infected with HCV significantly lower HCV RNA levels in the blood [17]. The change in serum HCV RNA levels after starting therapy is an important predictor of treatment outcome [18–20]. Especially, a 2-log reduction in the HCV RNA viral load by week 4 is a prerequisite to achieving SVR with PEG-

Table 5. Correlation between SVR and IL28B, RVR of previously relapsed patients

	SVR (n = 7)	Non-SVR (n = 11)	p value
RVR/non-RVR	7/0	1/10	0.0011
IL28B (major/minor)	6/1	7/4	0.3235

Bold p values are significant.

Table 6. Correlation between SVR and IL28B, RVR of previously NVR patients

	SVR (n = 3)	Non-SVR (n = 19)	p value
RVR/non-RVR	0/3	1/18	0.8636
IL28B (major/minor)	2/1	3/16	0.1169

IFN/RBV combination therapy [21]. Thus, the potential for effective IFN therapy combined with early physical removal of the virus is of particular interest.

Combined DFPP and IFN/RBV therapy contributes to early virological response and achieves high SVR [4, 22]. In the current study, although a 2-log reduction in the HCV RNA viral load by week 4 was observed in 61.5% of patients, RVR and SVR was observed in 23 and 25%, respectively. A previous study has concluded that relapsed patients would be better candidates for DFPP therapy than NVR patients in view of a significant difference in viral reduction at 24 and 48 h, and by weeks 1, 2, 4, 8 and 12, between NVR and relapsed patients [23]. In the current study, although a significant difference was observed in RVR between NVR and relapsed patients, no significant difference in SVR was apparent between them.

Factors predictive of virological response to PEG-IFN/RBV combination therapy have been reported in patients infected with high viral loads of genotype HCV-1b. IL28B major genotype (TT) as a host factor, a high degree (≥ 6) of sequence variation in IRRDR and a high degree (≥ 2) of sequence variation ISDR as viral factors have independently been demonstrated as significant pretreatment predictors of host- or viral-related factors [8–10, 14–16, 24, 25]. Multivariate analysis in our study showed that IL28B was the only significant pretreatment predictor of SVR in DFPP therapy, whereas IRRDR and ISDR were not significantly associated with SVR; RVR was, however,

significantly associated with SVR. RVR was also significantly related to SVR in the previously relapsed group. Patients achieving RVR have a high likelihood of achieving SVR by PEG-IFN/RBV combination therapy [26, 27]. Our study also suggested that achievement of RVR is essential for achieving SVR.

The recently accepted triple combination therapy comprising PEG-IFN, RBV and protease inhibitors such as telaprevir has shown that SVR is attained in 88% of relapse and 34% of NVR patients [28]. In the current study, SVR was achieved in 39% of relapse and 14% of NVR patients. Thus, combination therapy of DFPP with IFN and RBV is considered inferior to triple therapy for difficult-to-treat CHC patients. Nonetheless, triple therapy entails frequent discontinuation attributed to adverse events such as anemia and skin eruption [29]. Therefore, DFPP with IFN and RBV could become an alternative treatment for CHC patients intolerant of the triple combination

therapy. Because of the small number of patients in our study, analysis in a large-scale multicenter study is needed to clarify this issue. In conclusion, we believe that patients with high viral loads of genotype HCV-1b whose HCV had not been eradicated by PEG-IFN/RBV are good candidates for treatment by DFPP combined with IFN/RBV provided they demonstrate IL28B major and have achieved RVR.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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