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Original Article

Nursing Support Increases the Efficacy of Interferon Therapy in Patients with Chronic Hepatitis C

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Nursing support might help patients with chronic hepatitis C (CHC) remain in good mental and physical condition during interferon (IFN) therapy. However, the effects of nursing support have not been studied adequately in this context. This case-control study evaluated the effects of nursing support during IFN therapy. Twenty-four CHC patients who received pegylated IFN and ribavirin were enrolled. Nurses advised patients on the maintenance of their mental and physical condition at weekly visits, based on the results of written questionnaires. An additional 24 patients who received IFN therapy without nursing support and who were matched for age, sex, platelet count, viral serogroup and IFN regimen were selected with propensity score matching as controls. The patients with nursing support during IFN therapy achieved higher sustained virological responses (79%) than those without nursing support (58%). Adherence to the IFN and ribavirin regimens at 24 weeks of therapy were slightly higher in the patients with nursing support than those without it, but these differences were not statistically significant. Adherence to ribavirin after 24 weeks of therapy was significantly higher in those with nursing support than those without it (93% and 66%, $p = 0.045$). These results suggested that nursing support services could contribute to the virological responses of CHC patients by promoting drug-regimen adherence.

Key words: chronic hepatitis C, nursing support, interferon therapy

Approximately 200 million people are infected with hepatitis C virus (HCV) worldwide, and many patients with chronic hepatitis C (CHC) may have life-threatening diseases such as cirrhosis and hepatocellular carcinoma (HCC) without being aware of it [1]. Interferon (IFN) is widely used in the treatment of CHC patients, and the combination treatment with pegylated IFN and ribavirin has improved sus-

tained virological response with a success rate of more than 50% [2, 3]. However, IFN has various adverse effects, such as psychological disturbances, poor appetite, skin rash, and thrombocytopenia [4]. According to a systematic review by Bota *et al.*, IFN treatment was discontinued in 14.5% of patients due to severe adverse events. Therefore, prevention or alleviation of adverse effects is important for IFN therapy.

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Several studies have reported that good drug adherence is needed for sustained virological response (SVR) to IFN therapy [5]. Recent reports have proposed that a management program or education by medical staff may improve drug adherence [6–9]. The outpatient viral hepatitis clinic in our hospital provides CHC patients with nursing support services during IFN therapy; nurses offer face-to-face counseling, based on the results of written questionnaires, at the weekly visits for IFN administration, and advise patients on the maintenance of their mental and physical health.

The present study investigated the relationships of therapeutic outcomes, drug adherence and physical and mental health to the provision of nursing support services in patients during IFN therapy.

Methods

Patients. This case-control study included 24 CHC patients who received combination therapy with pegylated IFN and ribavirin at our hospital between 2010 and 2012. The viral hepatitis outpatient clinic at our hospital provided them with nursing support during IFN therapy. Among the patients who received IFN therapy between 2008 and 2010 without nursing support, 24 patients, matched for age, sex, platelet count, viral serogroup and IFN regimens, were selected with propensity score matching as a control group. Health-related quality of life, including both mental and physical components, was evaluated prior to therapy for all patients using the 36-item short-form health survey version 2. These written questionnaires consist of 8 subscales, with each subscale having been adjusted so that a score of 50 corresponds to the mean value for that subscale in the general Japanese population [10]. Patients with liver transplantations or co-infection with hepatitis B virus or human immuno-deficiency virus were excluded. The present study was performed in accordance with the Helsinki declaration, and the protocol was approved by the ethics committee of our institute. All the patients provided informed consent.

Therapeutic regimens. The therapeutic regimens included weekly subcutaneous administration of 180 μ g of pegylated IFN- α 2a or 1.5 μ g per body weight of pegylated IFN- α 2b plus twice-daily oral intakes of ribavirin at a dose based on body weight. The dura-

tion of IFN therapy was determined based on the viral serogroup, viral load, and virological response of the patients, for 24 to 72 weeks, as recommended in the guidelines for the management of HCV infection in Japan [11]. The doses of IFN and ribavirin were individually reduced during the therapy whenever needed to lessen adverse effects, and the dose reductions were performed according to the labeling.

Nursing support services. Each time the patients visited the viral hepatitis outpatient clinic for IFN administrations during IFN therapy, they answered a written questionnaire assessing their physical condition with respect to 10 adverse events during IFN therapy: increased fever, body pain, appetite loss, malaise, eruption, palpitation, cough, dizziness, sleep disturbance, and anxiety. Each of these potential events was graded using a 5-point scale. An increase in the sum of these scores indicated poorer physical condition. The Beck Depression Inventory of 21 questions was also used to assess their mental conditions [12, 13]. Three nurses, who received monthly training via conference on the treatments for liver diseases and who each had more than 3 years of experience in caring for patients in a hepatitis clinic, offered face-to-face counseling to the patients at every visit, based on the results of the written questionnaires. They also provided the patients with further education on their liver diseases, and helped them to maintain their motivations for continuing IFN therapy.

Statistical methods. Data are expressed as the median \pm standard error. Caliper matching was performed on the propensity scores that had absolute values less than 10% different. Patient characteristics and changes in mental and physical condition were compared between the 2 groups using the Mann-Whitney U test and Fisher's exact probability test. A value of $p < 0.05$ was considered significant.

Results

Patient characteristics. Table 1 shows the comparisons of patient characteristics between the group with and that without nursing support during IFN therapy. Each group consisted of 24 patients matched for age, sex, platelet count, viral serogroup, IFN regimens, and history of previous IFN therapy; 19 patients were male, and 12 patients (50%) had HCV serotype 1. The median ages were 62 years and

Table 1 Characteristics of the enrolled patients

Patient characteristics	Nursing support		<i>p</i>
	+	-	
Age (years)	62 ± 2 [‡]	60 ± 2 [‡]	
Gender (male/female)	19/5	19/5	
HCV serogroup (1/2)	12/12	12/12	
Therapy regimen (IFN+RBV/IFN)	21/3	21/3	
Platelet count (10000/mm ³)	17 ± 1 [‡]	16 ± 1 [‡]	
Hemoglobin (g/dL)	13.6 ± 0.2 [‡]	13.4 ± 0.5 [‡]	0.91
Alanine aminotransferase (IU/L)	40 ± 11 [‡]	45 ± 10 [‡]	0.55
Body weight (kg)	53 ± 2 [‡]	56 ± 1 [‡]	0.55
HCV RNA (Log IU/mL)	6.3 ± 0.2 [‡]	6.2 ± 0.1 [‡]	0.60
Health-related quality of life			
Physical function	53 ± 2 [‡]	53 ± 2 [‡]	0.94
Role-physical	46 ± 4 [‡]	49 ± 4 [‡]	0.74
Bodily pain	54 ± 2 [‡]	54 ± 2 [‡]	1.00
General health	45 ± 2 [‡]	46 ± 2 [‡]	0.82
Vitality	50 ± 2 [‡]	49 ± 2 [‡]	0.87
Social function	44 ± 3 [‡]	44 ± 3 [‡]	0.91
Role-emotional	42 ± 3 [‡]	44 ± 3 [‡]	0.76
Mental health	44 ± 2 [‡]	45 ± 2 [‡]	0.87

‡ : Median ± standard error. HCV, hepatitis C virus; IFN, interferon; RBV, ribavirin.

60 years, respectively. There were no significant differences between the 2 groups in terms of hemoglobin levels, alanine aminotransferase, or body weight. The mental and physical conditions of patients prior to IFN therapy were also not significantly different between the 2 groups.

Virological response to IFN therapy. Among the patients with nursing support during IFN therapy, 19 patients obtained SVR, while 3 patients relapsed after IFN therapy, and 2 patients showed partial or null virological responses to IFN therapy. On the other hand, SVR was observed in 14 of the 24 patients who had no nursing support during IFN therapy, with 5 of the remaining patients showing relapse after IFN therapy, and 5 showing partial or null virological responses to IFN therapy. The patient group with nursing support during IFN therapy had a slightly higher SVR rate (79%) than the group without nursing support (58%), but this difference was not statistically significant ($p = 0.21$, Fisher's exact probability test).

Adherence to the IFN and ribavirin regimens during IFN therapy. The patients with nursing support during IFN therapy exhibited better adherence to their IFN and ribavirin regimens (92% of

scheduled IFN and 86% of scheduled ribavirin doses) than those without nursing support (79% of IFN and 75% of ribavirin doses), although these differences were not statistically significant. The patients with nursing support during IFN therapy had better drug adherence to IFN and ribavirin from 0 to 24 weeks of treatment, and to IFN from 24 weeks and beyond, than those without nursing support, although these differences were not statistically significant ($p = 0.43$, $p = 0.13$, and $p = 0.11$, respectively; Fig. 1). Drug adherence to ribavirin in the latter therapeutic period after 24 weeks of IFN therapy was significantly higher in those with nursing support than those without it (93%, and 66%, $p = 0.045$).

Changes in mental and physical condition during IFN therapy. Changes in the status of physical and mental health during IFN therapy are summarized in Fig. 2. Mental and physical conditions were worsened between 12 and 24 weeks of the therapy, and poor conditions continued thereafter. The changes in mental and physical health status during IFN therapy seemed to differ between SVR and non-SVR patients; SVR patients had higher scores (*i.e.*, poorer conditions) at baseline, and showed greater increases in their scores during IFN therapy than non-

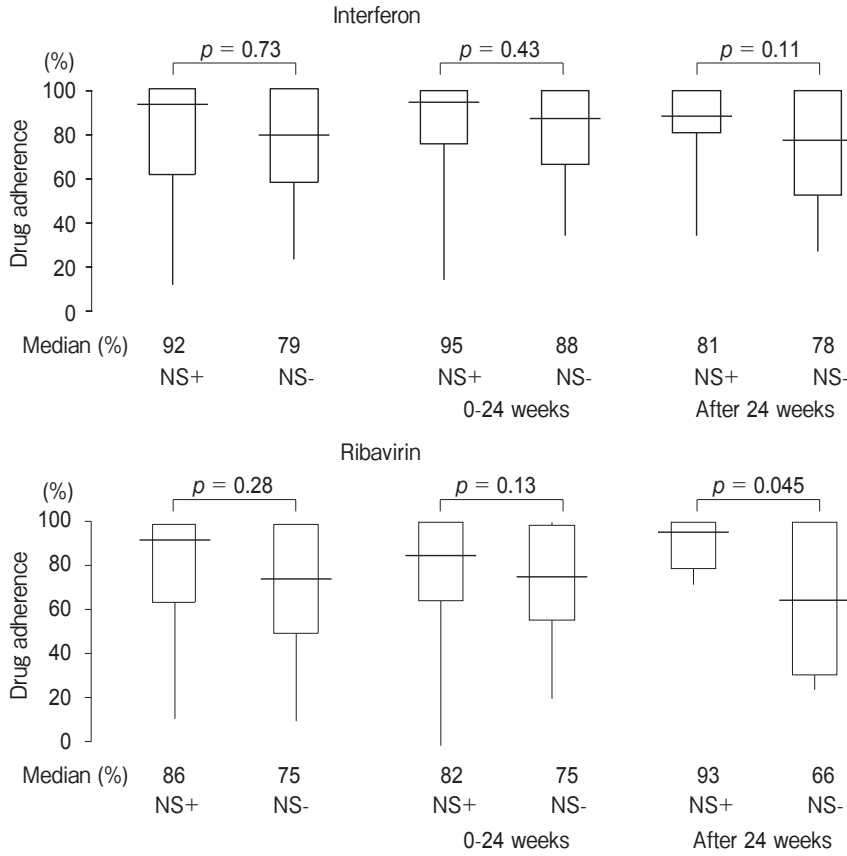


Fig. 1 Adherence to the IFN and ribavirin regimens during IFN therapy. The percentages of patients complying with the IFN and ribavirin treatments during IFN therapy were calculated. The figure expresses the quintiles and medians of drug adherence to the IFN and ribavirin regimens from 0 to 24 weeks of treatment and from 24 weeks and beyond, respectively, for the patients with and without nursing support during IFN therapy. NS+, the patients with nursing support during IFN therapy; NS-, the patients without nursing support during IFN therapy.

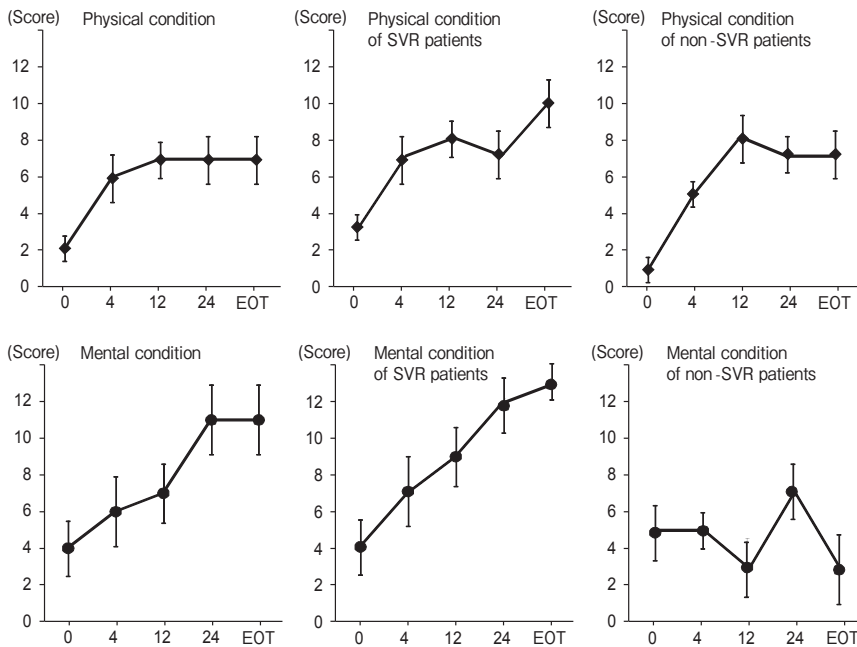


Fig. 2 Changes in mental and physical condition during IFN therapy. Physical condition was evaluated with a physical condition score at every visit for IFN injections, and mental condition was assessed by BDI. The figures show the changes in the mental and physical condition of the patients with nursing support during IFN therapy. EOT, the end of IFN therapy.

SVR patients, which was consistent with the previous report [14]. To clarify this inverse relationship between therapeutic outcomes and patient conditions, we further investigated the associations between nursing support and supplemental medications. Supplemental medications consisted only of the drugs for additional treatments for side effects during IFN therapy. Our results revealed that the number of supplemental drugs by 24 weeks of IFN therapy was significantly greater among the patients with nursing support (11 drugs) than those without it (5 drugs, $p < 0.01$). The situation was similar thereafter (8 drugs in the patients with nursing support, and none in those without nursing support, $p < 0.01$).

Discussion

It was previously reported that nursing support during IFN therapy might contribute to virological response by improving drug adherence. However, the precise associations between nursing support and drug adherence during IFN therapy have not been studied. In the present case-control study, we enrolled 24 patients who received IFN therapy with nursing support, and compared their therapeutic outcomes and drug adherence to those of 24 control patients who received IFN therapy without nursing support. The controls were matched with the subject group for baseline characteristics with propensity score matching. The results clarified that precise assessments of a patient's physical and mental health status by a nurse may help in the maintenance of drug adherence when the patients suffer from poor mental condition, and thus nursing support may improve the virological responses of CHC patients.

Previous studies have suggested that education on IFN therapy by a specialized nurse or a medical staff member increases the virological response of CHC patients, particularly difficult-to-treat patients [6–9]. However, these studies have not clarified the associations between nursing support services and either drug adherence or other therapy-associated factors. Through the observation of patients who received nursing support services during IFN therapy, we found that SVR patients had worse mental and physical health status during IFN therapy than non-SVR patients. This is important, since it has been reported that patients sometimes reduce or stop drug administration when

they feel worse [15]. Continuously worsening conditions thus might pose a risk of lowered drug compliance. Nursing support can help patients to better understand the side effects of their drugs and the necessity of good drug compliance. An improved understanding of their liver diseases may encourage patients to more clearly explain any unpleasant effects they are experiencing. This, in turn, would enable the precise assessment of individual patients by nurses, and the supply of appropriate supplemental medications by doctors. Our results revealed that the number of supplemental drugs was significantly greater among the patients with nursing support during IFN therapy than those without it, and suggested that the administration of supplemental drugs to alleviate adverse events is helpful to maintain adherence to the IFN and ribavirin regimens.

The number of patients was limited in the present study, and we could not verify the impact of nursing support in comparison with other factors affecting therapeutic outcomes such as host and viral factors [14, 16, 17]. The impact of nursing support should be explored in future large scale studies.

In conclusion, the present study revealed that precise assessments of the mental and physical condition of individual patients by a nurse might promote maintenance of a drug regimen in cases where such conditions are poor. Nursing support might thereby contribute to the virological responses of CHC patients by promoting continued drug compliance.

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