INTRODUCTION

Globally, hepatitis C virus (HCV) infection is the most frequent cause of chronic liver disease; approximately 2.2% of adults worldwide are chronically infected with HCV. Despite recent advances in direct-acting antivirals (DAAs), combined treatment with pegylated interferon-α (PEG-IFN-α) and ribavirin (RBV) is still regarded as the standard backbone treatment for chronic hepatitis C (CHC), due to the considerably high cost of DAAs, especially in developing countries. Psychiatric adverse events, including depression, fatigue, cognitive impairment, and insomnia, are frequently encountered to varying degrees during PEG-IFN-based treatment. In general, PEG-IFN-α-based treatment for CHC usually induces depression in 20–40% of patients with CHC. The clinical symptoms associated with IFN-induced depression are analogous to those seen in major depressive disorder (MDD). Since IFN-induced depressive symptoms usually limit the IFN dosage, they may compromise antiviral efficacy and bring substantial distress to some patients with CHC. Furthermore, moderate-to-severe depressive symptoms often lead to treatment delays or premature withdrawal from antiviral therapy, with a strong negative impact on quality of life (QOL).

Although depressed mood is one of the core symptoms of MDD, this symptom may not be as prominent in patients with...
The diagnosis of CHC was made on the basis of seropositivity prospective cohort between August 2011 and November 2013. The primary aim of this study was to investigate prospectively every 4 weeks for the entire treatment period. After collecting baseline psychiatric measurements, PEG-IFN-α-2a (fixed dose, 135 or 180 μg) was injected subcutaneously weekly and oral RBV was administered twice daily based on patient body weight (1.0 g, ≤75 kg; 1.2 g, >75 kg) for patients with genotype 1. A fixed dose (0.8 g) of RBV was given to those with genotype 2. Treatment duration differed according to HCV genotypes: antiviral treatment was maintained for 48 weeks in patients infected with HCV genotype 1 and for 24 weeks in those with genotype 2. Study participants were followed every 4 weeks during PEG-IFN/RBV treatment, with a physical examination, laboratory testing, and assessments of subjective adverse events conducted at each visit. PEG-IFN-α-2a was discontinued when the absolute neutrophil count was <500/mL or the platelet count was <25,000/mm³. If anemia (hemoglobin <8 g/dL) was persistent during combination therapy, RBV was withdrawn gradually according to the manufacturer’s recommendations.

Study design
Patients with CHC and without depressive disorder who were started on antiviral therapy with PEG-IFN-α-2a plus RBV were examined at baseline and then followed prospectively every 4 weeks for the entire treatment period. After collecting baseline psychiatric measurements, PEG-IFN-α-2a (fixed dose, 135 or 180 μg) was injected subcutaneously weekly and oral RBV was administered twice daily based on patient body weight (1.0 g, ≤75 kg; 1.2 g, >75 kg) for patients with genotype 1. A fixed dose (0.8 g) of RBV was given to those with genotype 2. Treatment duration differed according to HCV genotypes: antiviral treatment was maintained for 48 weeks in patients infected with HCV genotype 1 and for 24 weeks in those with genotype 2. Study participants were followed every 4 weeks during PEG-IFN/RBV treatment, with a physical examination, laboratory testing, and assessments of subjective adverse events conducted at each visit. PEG-IFN-α-2a was discontinued when the absolute neutrophil count was <500/mL or the platelet count was <25,000/mm³. If anemia (hemoglobin <8 g/dL) was persistent during combination therapy, RBV was withdrawn gradually according to the manufacturer’s recommendations.

Methods
Study participants
Patients aged 20 to 75 years with CHC at Seoul Metropolitan Government Seoul National University (SMG-SNU) Boramae Medical Center were consecutively enrolled in the prospective cohort between August 2011 and November 2013. The diagnosis of CHC was made on the basis of seropositivity for anti-HCV antibodies and detectability of HCV RNA in sera before starting antiviral therapy, irrespective of aminotransferase levels. CHC patients treated with PEG-IFN-α-2a (Pegasys; Hoffmann-La Roche Inc., Basel, Switzerland) combined with ribavirin (RBV) were eligible for this prospective cohort study. Those with the following conditions were excluded: previous treatment with IFN-α or PEG-IFN; chronic liver disease other than CHC such as seropositivity for hepatitis B surface antigen, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, and Wilson disease; decompensated liver cirrhosis (Child-Pugh class B or C); heavy alcohol consumption (≥20 g/day); previous liver transplantation; presence of hepatocellular carcinoma; psychiatric disease including depression; overt hypo- or hyperthyroidism at baseline; platelets <90,000/mm³; hemoglobin <12 (men) or <11 (women) g/dL; neutrophils <1,500/mm³; and serum creatinine ≥1.5 mg/dL. Pregnant and nursing women were also excluded. The study was approved by the SMG-SNU Boramae Medical Center Institutional Review Board (IRB No. 06-2011-130), and it complied with the ethical guidelines of the 1975 Declaration of Helsinki. Written informed consent was obtained from all study participants who were enrolled in this prospective cohort study. This investigation is registered as “NCT01465919” (http://clinicaltrials.gov).

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Interferon Induced Depression and Distress

Five model evaluates five dimensions of personality: neuroticism (includes traits such as being tense, moody, and anxious), extraversion (includes traits such as being talkative, assertive, and energetic), agreeableness (includes traits such as being sympathetic, affectionate, and kind), openness to experience (includes traits such as having wide-ranging interests and being imaginative and insightful), and conscientiousness (includes traits such as being organized, thorough, and competent). A brief explanation of these five personality constructs is covered elsewhere.27

To measure impulsivity as one of the personality dimensions, we used the Korean version of the Barratt Impulsiveness Scale, version 11 (BIS-11).30,31 The BIS-11 consists of three factors: cognitive impulsiveness (making quick decisions), motor impulsiveness (acting without thinking), and nonplanning impulsiveness (a lack of “futura” or foresight).32,33

We used the behavioral inhibition system (BIS) and behavioral activation system (BAS) scales to assess sensitivity to rewards and punishment.4 The BIS and BAS scales consist of 20 items rated on a four-point Likert scale from “totally agree” to “totally disagree.” The BIS and BAS scales consist of 7 and 13 items, respectively. The BAS scale can be subdivided into three subscales: fun seeking (BAS-fun; four items), reward responsiveness (BAS-reward; five items), and drive (BAS-drive; four items).

Histological and mechanical assessment of liver fibrosis

Study participants underwent liver biopsy within 4 weeks prior to the start of antiviral treatment. The META-analysis VIRus hepatitis histological scoring system (METAVIR) was used to assess the histological fibrosis stage for hepatitis C.27 Simultaneously, liver stiffness as a mechanical fibrosis indicator was measured by means of acoustic radiation force impulse (ARFI) elastography (Acuson S2000; Siemens AG, Erlangen, Germany) as described elsewhere.26

Prospective evaluation

After initiating antiviral therapy, we conducted a self-report questionnaire survey that included BDI, BAI, K-POMS, and PWI regularly every 4 weeks during PEG-IFN-α-2a-based treatment. IFN-induced depressive disorder was categorized as either MDD or subsyndromal depression. A trained psychiatrist meticulously evaluated all study participants and diagnosed them with MDD or subsyndromal depression, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV, using the SCID. A diagnosis of subsyndromal depression was made if there were two or more simultaneous symptoms listed in the DSM-IV depressive episode criteria. These symptoms must have been present at all times for at
least 2 weeks and have been associated with evidence of functional dysfunction. Additionally, the individual must not have met the criteria for a diagnosis of major depression. The incidence of MDD was diagnosed with a HAMD-17 score of ≥14 as well as the DSM-IV major depressive episode criteria. The severity of depressive disorder was also assessed by means of HAMD-17. To determine antiviral treatment response, sustained virological response (SVR) was defined as undetectable serum HCV RNA by quantitative PCR at 24 weeks after the completion of treatment. Relapse was defined as an increase in serum HCV RNA titer after achieving end of treatment response (ETR).

Statistical analysis

Demographic and clinical variables are expressed as mean± standard deviation (SD) or frequencies and proportions (%). The two-sample t-test for continuous variables and the χ² test or Fisher's exact test for categorical variables were used for group comparisons. More information about several psychiatric mood symptoms was obtained repeatedly throughout IFN-based treatment. To evaluate the sequential change in mood symptoms over time, a linear mixed-effects model for repeated measures from same subjects was used, which uses all available data and provides the valid results in the presence of missing data under the assumption that missing data are missing at random. Differences between nondepressed patients and those with major depression, and between patients with genotype 1 and those with genotype 2 over time were also compared using the linear mixed-effects model. The model considered sex, age, status of major depression, time, and status-by-time interaction as fixed effects and incorporated a random intercept effect. For multiple comparisons, the Bonferroni correction was universally applied. In addition, logistic regression analysis was conducted to assess whether psychiatric, personality, or HCV-related factors contributed to the development of depressive disorder. P values of <0.05 were considered statistically significant. All statistical analyses were performed with IBM SPSS Statistics version 20 (IBM Inc., Chicago, IL, USA) and R version 3.1.0 (http://www.r-project.org).

RESULTS

Demographic and clinical data

A total of 69 treatment-naïve patients with HCV were included in the prospective cohort study. Of these, two patients declined to participate in the study. The most predominant genotypes of HCV are 1b or 2a/c in Korean patients with hepatitis C. In the current study, all study participants were treated with PEG-IFN-α-2a plus RBV for 48 (HCV genotype 1b, n=29) or 24 (HCV genotype 2a/c, n=38) weeks. Table 1 shows the demographic and clinical characteristics of all study subjects. There were no significant differences in age, sex ratio, body mass index (BMI), baseline PWI, measures of personality, HCV genotype, liver stiffness, METAVIR fibrosis stage, or initial IFN dose between patients with IFN-induced depression and those without depression. Although mood status scores for all subjects were within the normal range for BDI and BAI, there were significant differences in BDI and BAI scores between the groups. In addition, there were also significant differences in K-POMS total and subscale scores (except tension-anxiety, anger-hostility, and vigor-activity) between the groups.

Evolution of depressive disorder during PEG-IFN-α-2a-based treatment

Of all subjects (n=67), 15 (22.4%) met the criteria for depressive disorder following initiation of IFN-based treatment. Seven subjects (10.4%) met the criteria for MDD, and eight (11.9%) fulfilled the criteria for subsyndromal depression. Times of onset of MDD and subsyndromal depression were 6.67±5.01 and 11.11±5.58 weeks, respectively, after initiation of IFN-based treatment. All susceptible patients developed depressive disorder within 20 weeks after initiation of IFN-based treatment. Mean scores of HAMD-17 at diagnosis of MDD and subsyndromal depression were 18.43±3.64 and 9.17±2.56, respectively. Of four patients with depressive disorder and HCV genotype 1, three dropped out prematurely and only one completed antiviral treatment for 48 weeks.

Time course of mood symptoms and level of distress

Among all participants, BDI and PWI scores did not change significantly during the course of PEG-IFN-α-2a-based treatment (Figure 1). However, the BAI score (Figure 1) and fatigue-inertia subscale of the K-POMS (Figure 2) showed significant changes in all participants during the course of antiviral treatment. Significant increases in the BAI score after initiation of PEG-IFN-α-2a-based treatment were found at 8 weeks (P<0.013), 16 (P=0.016), and 20 (P<0.017) weeks compared to the baseline BAI score. A significant increase in the fatigue-inertia subscale score of the K-POMS was found at 8 weeks (P=0.018) compared to the baseline score.

Figures 3 and 4 show the temporal kinetics of mood symptoms and level of distress in patients with MDD and those with no depression. There were significant differences in the BDI score from baseline through 28 weeks between patients with MDD and those without depression. The peak time for an increase in the BDI score after initiation of PEG-IFN-α-2a-based treatment was 16 weeks (least squares mean of BDI score=24.09). There were significant differences in the BAI
### Table 1. Demographic and clinical characteristics of study subjects

| Variables                          | Total (N=67) | Depression (N=15) | Non-depression (N=52) | p value |
|------------------------------------|--------------|-------------------|-----------------------|---------|
| **Baseline characteristics**       |              |                   |                       |         |
| Age, years                         | 55.45±11.23  | 57.8±18.18        | 54.77±11.95           | 0.361   |
| Sex (M/F), N (%)                   | 32 (47.60)/35 (52.44) | 7 (46.67)/8 (53.33) | 25 (48.08)/27 (51.92) | 0.923   |
| BMI, kg/m²                         | 23.26±2.93   | 24.08±2.2         | 23.02±3.09            | 0.222   |
| Baseline BDI                       | 4.64±5.5     | 7.47±5.05         | 3.83±5.39             | 0.023*  |
| Baseline BAI                       | 4.49±5.67    | 7.93±6.94         | 3.32±4.71             | 0.007*  |
| Baseline PWI                       | 44.11±21     | 53.21±22.11       | 40.85±19.87           | 0.058   |
| **Baseline K-POMS**                |              |                   |                       |         |
| Total                              | 38.91±28.2   | 57.43±33.19       | 32.26±23.23           | 0.003*  |
| Tension-anxiety                    | 3.94±4.03    | 6.36±5.88         | 3.08±2.74             | 0.063   |
| Depression-dejection               | 6.36±9.88    | 11.07±11.36       | 4.67±8.85             | 0.036*  |
| Anger-hostility                    | 2.94±4.66    | 5.93±7.17         | 1.87±2.75             | 0.058   |
| Vigor-activity                     | 8.53±8.03    | 9.5±8.47          | 8.18±7.95             | 0.602   |
| Fatigue-inertia                    | 4.45±4.86    | 7.07±5.74         | 3.51±4.2              | 0.017*  |
| Confusion-bewilderment             | 4.02±3.75    | 6±4.17            | 3.33±3.38             | 0.020*  |
| **NEO-PI-R**                       |              |                   |                       |         |
| Agreeableness                      | 43.6±7.53    | 41.93±8.39        | 44.21±7.21            | 0.336   |
| Conscientiousness                  | 41.74±9.26   | 41.93±9.12        | 41.67±9.43            | 0.929   |
| Extraversion                       | 37.55±7.6    | 35.86±7.23        | 38.15±7.73            | 0.337   |
| Neuroticism                        | 29.94±8.32   | 31±7.49           | 29.56±8.65            | 0.584   |
| Openness to experience             | 35.19±6.91   | 34.21±8.37        | 35.54±6.39            | 0.543   |
| **BIS**                            |              |                   |                       |         |
| Total                              | 40.36±11.08  | 42.71±10.84       | 39.51±11.18           | 0.359   |
| Reward dependence                  | 40.36±11.08  | 42.71±10.84       | 39.51±11.18           | 0.359   |
| Drive                              | 10.68±3.64   | 10.71±4.07        | 10.67±3.53            | 0.967   |
| Fun seeking                        | 8.02±3.03    | 8.86±3.3          | 7.72±2.92             | 0.232   |
| **BIS-11**                         |              |                   |                       |         |
| Total                              | 55.04±11.71  | 56.07±10.95       | 54.67±12.08           | 0.704   |
| Cognitive                          | 16.87±3.62   | 16.36±4.03        | 17.05±3.49            | 0.543   |
| Motor                              | 16.13±5.42   | 17±4.67           | 15.82±5.69            | 0.490   |
| Non-planning                       | 22.04±5.24   | 22.71±5.44        | 21.79±5.22            | 0.579   |
| Genotype (1/2), N (%)              | 29 (43.28)/38 (56.72) | 4 (26.67)/11 (73.33) | 25 (48.08)/27 (51.92) | 0.140   |
| Liver stiffness, m/s               | 1.72±0.58    | 1.76±0.54         | 1.71±0.59             | 0.826   |
| **METAVIR stage,**† N (%)          |              |                   |                       | 0.089   |
| 0                                  | 2 (3.51)     | 1 (7.69)          | 1 (2.27)              |         |
| F1                                 | 19 (33.33)   | 2 (15.38)         | 17 (38.64)            |         |
| F2                                 | 15 (26.32)   | 4 (30.77)         | 11 (25.00)            |         |
| F3                                 | 7 (12.28)    | 4 (30.77)         | 3 (6.82)              |         |
| F4                                 | 14 (24.56)   | 2 (15.38)         | 12 (27.27)            |         |
| Initial IFN dose, N (%)            |              |                   |                       | 1.000   |
| 135 μg                             | 13 (19.40)   | 3 (20.00)         | 10 (19.23)            |         |
| 180 μg                             | 54 (80.60)   | 12 (80.00)        | 42 (80.77)            |         |
score from baseline through 28 weeks between patients with MDD and nondepressed patients. Degree of distress, as measured by PWI, showed two peak times, with an increase in the score at 8 and 24 weeks, indicating higher levels of distress in patients with IFN-induced MDD (Figure 3). There were significant differences in K-POMS subscale scores for tension-anxiety, depression-dejection, anger-hostility, fatigue-inertia, and confusion-bewilderment from 4 weeks through 28 weeks between patients with IFN-induced MDD and those without depression (Figure 4). However, there were no significant differences in BDI, BAI, PWI, and K-POMS subscale scores during the first 24 weeks of treatment between patients with genotype 1 and those with genotype 2.

Predictors of evolution of depressive disorder

To find factors predictive of the development of depressive disorder following PEG-IFN-α-2a-based treatment, logistic regression analysis was conducted between variables, including demographic, psychiatric, personality, and HCV-related characteristics, and depressive disorder. Logistic regression analysis showed that BDI, BAI, and K-POMS total scores at pretreatment were significant predictors of the onset of depressive disorder [BDI: odds ratio (OR) 1.14, 95% confidence interval (CI) 1.02–1.27, p=0.025, BAI: OR 1.15, 95% CI 1.03–1.29, p=0.017, and K-POMS total: OR 1.04, 95% CI 1.01–1.07, p=0.010]. In addition, K-POMS subscales (except vigor-hostility) also predicted the development of depressive disorder (data not shown). Level of distress at baseline tended to predict the onset of depressive disorder, although it did not reach statistical significance (PWI: OR 1.03, 95% CI 1.00–1.07, p=0.067).

Other psychiatric and personality traits, as well as HCV-related factors, including HCV genotype, liver stiffness, METAVIR stage, and initial IFN dose, did not predict the onset of depressive disorder significantly.

Relationship between IFN-induced depressive disorder and antiviral treatment response or treatment adherence

There was no significant association between IFN-induced depressive disorder and SVR or relapse rate (Table 1). With respect to dropout rate, of patients with depressive disorder (n=15), six (40.0%) dropped out prematurely after initiation of IFN-based treatment, whereas 28.8% of nondepressed patients with HCV dropped out of IFN-based treatment. The main reason for dropout in patients with depressive disorder (four out of six) was the depressive disorder itself.

Table 1. Demographic and clinical characteristics of study subjects (continued)

| Variables | Total (N=67) | Depression (N=15) | Non-depression (N=52) | p value |
|-----------|--------------|-------------------|----------------------|---------|
| IFN-induced response characteristics, N (%) | | | | |
| SVR | 42 (62.69) | 10 (66.67) | 32 (61.54) | 0.718 |
| Relapse | 17 (29.82) | 4 (26.67) | 13 (30.95) | 0.906 |

*p<0.05; histologic data of liver biopsy were available in 57 patients (85.1%). BMI: Body Mass Index, BDI: Beck Depression Inventory, BAI: Beck Anxiety Inventory, PWI: Psychosocial Well-being Index, K-POMS: Korean version of Profile Of Mood States, NEO-PI-R: Neuroticism-Extraversion-Openness Personality Inventory Revised, BIS: Behavioral Inhibition System, BAS: Behavioral Activation System, BIS-11: Barratt Impulsiveness Scale-Version 11, METAVIR: META-analysis VIRus hepatitis histologic scoring system, IFN: Interferon, SVR: Sustained Virological Response.
DISCUSSION

The present study tracked the prospective course of mood symptoms and level of distress in patients with HCV infection every 4 weeks during PEG-IFN-α-2a-based treatment and investigated comprehensively the relationship between the development of depressive disorder and clinical, psychiatric, and personality traits.

We found that 22.4% (n=15) of patients treated with PEG-IFN-α-2a/RBV met the criteria for depressive disorder following initiation of IFN-based treatment. Of patients with depressive disorder, 10.4% (n=7) met the diagnostic criteria for MDD and 11.9% (n=8) fulfilled criteria for subsyndromal depression. In line with previous reports, IFN-based treatment was accompanied by a significant increase in depressive symptoms in our study. Previous studies reported that depressive symptoms are common in the early stage of antiviral treatment and reach peak levels at 4–16 weeks. Hauser et al. also found that depression developed rapidly in patients with CHC during IFN-based treatment. In 62% (8/13) of patients who developed IFN-induced MDD, BDI scores increased from ≤10 to ≥18 within 2 weeks. In the present study, we found that onset of depressive disorder after initiation of IFN-based treatment was approximately 9.33 ± 5.64 weeks. Furthermore, MDD developed relatively earlier than did subsyndromal depression, although this was not statistically significant (6.67 ± 5.01 and 11.11 ± 5.58 weeks, respectively). In accordance with the aforementioned findings, onset of depressive disorder was seen in the early stage of antiviral treatment. A possible explanation for the development of depressive disorder resulting from IFN-based treatment is that IFN induces a surge in the activity of indoleamine 2, 3-dioxygenase (IDO), which is a tryptophan (TRP)-catabolizing enzyme, leading to greater breakdown of TRP to kynurenine (KYN). Thus, a markedly

Figure 2. Time course of scores in Korean version of Profile of Mood States (K-POMS; A: tension-anxiety, B: depression-dejection, C: anger-hostility, D: vigor-activity, E: fatigue-inertia, F: confusion-bewilderment) in all patients during interferon-based treatment. *p<0.05; horizontal bar represents standard error.
reduced concentration of TRP is available for serotonin synthesis in the brain. Baranyi et al. reported that a decrease in TRP availability in the brain, as well as an increase in neurotoxic challenge, develops in patients with depression during IFN-based treatment. A notable neurotoxic challenge due to the accumulation of KYN metabolites was found in patients with depression during the first several months after initiation of IFN-based treatment. The aforementioned biological alterations could support the development of depressive disorder in the earlier stages of IFN-based treatment. Accordingly, clinicians should be vigilant for the presence of depressive symptoms during the early stage of IFN-based treatment.

In the current study, all patients with chronic HCV infection showed significant changes in fatigue, among the various depressive symptoms, during the course of IFN-based treatment. Furthermore, fatigue at pretreatment predicted the onset of subsequent IFN-induced depressive disorder. According to Shakoor et al., fatigue or loss of energy was the second most common symptom, following loss of interest, in patients with depressive disorder induced by IFN-based treatment. Furthermore, fatigue might be a more common symptom than depressed mood itself. Lofts et al. reported that an increase in depressive symptoms during IFN-based treatment is the result of significant increases in somatic symptoms. Moreover, when present, somatic symptoms can interfere with both successful completion of IFN-based treatment and steady maintenance of QOL. Therefore, it is of critical importance to pay attention to somatic symptoms, especially fatigue, and to manage them actively during IFN-based treatment.

Stress is the body’s reaction to changes that require a physical, mental, or emotional adjustment or response. Controlling stress is important to health, and stress that continues without relief can lead to a condition called distress, a negative stress reaction. Distress can disturb the body’s internal balance or equilibrium, leading to physical symptoms such as headache, upset stomach, elevated blood pressure, chest pain, sexual dysfunction, and problems sleeping. Emotional problems such as anxiety and worry can also result from distress. Higher levels of distress are also associated with lower QOL. In the present study, patients who developed MDD showed higher levels of distress during IFN-based treatment. The pretreatment level of distress, as measured by PWI, was associated with the subsequent depressive disorder at a trend level. Therefore, stress management may be helpful in preventing IFN-induced depressive disorder, as well as in improving psychological well-being in patients with hepatitis C receiving PEG-IFN-α-2a/RBV.

In the present study, we examined risk factors associated with the development of depressive disorder during IFN-based treatment. The identification of risk factors for depressive disorder may assist in detecting high-risk patients who may benefit from psychological support and in improving the QOL of patients receiving IFN-based treatment. We comprehensively evaluated various kinds of risk factors, including personality, pretreatment mood states, degree of stress, and HCV-related characteristics. Pretreatment BDI, BAI, and K-POMS scores were significant predictors of IFN-induced depressive disorder. Udina et al. reported that clinical factors, such as baseline subthreshold depressive symptoms, are associated with a higher incidence of major depressive episode.
during antiviral treatment, along with the presence of a past depressive or psychiatric disorder. Although subjects included in the present study had no previous or current psychiatric disorders, pretreatment subthreshold depression, anxiety, or somatic symptoms could increase the likelihood of developing depressive disorder during the course of PEG-IFN-α-2a-based treatment. We did not find significant associations between specific personality traits and the development of depressive disorder. However, previous studies reported that individuals with higher neuroticism, lower agreeableness, or lower self-directedness may be more likely to suffer depression.

According to our findings and those of previous studies, it is important to screen and monitor mood symptoms before and during IFN-based treatment to enhance psychological well-being as well as adherence to IFN-based treatment. The association between the development of depressive disorder and

Figure 4. Time course of scores in Korean version of Profile of Mood States (K-POMS; A: tension-anxiety, B: depression-dejection, C: anger-hostility, D: vigor-activity, E: fatigue-inertia, F: confusion-bewilderment) in patients with major depressive disorder and those without depression during interferon-based treatment. As there was only one patient with depressive disorder and HCV genotype 1 who completed antiviral treatment for 48 weeks, this figure expressed data from baseline through 28 weeks. *p<0.05, **p<0.01, ***p<0.001; horizontal bar represents standard error. HCV: hepatitis C virus.
adherence to IFN-based treatment was also supported by the present study. Patients with depressive disorder showed higher rates of dropout due to the depressive disorder itself compared to other reasons for dropout. With respect to the influence of depression on the response to IFN-based treatment (i.e., SVR or relapse rate), we could not find any significant association between the development of depressive disorder and IFN responsiveness. However, once depressive disorder develops, it may adversely affect adherence to IFN-based treatment.

The strengths of our study are its prospective design, with monthly time points during IFN-based treatment, and our exploration of the relationship between psychiatric factors, including personality and degree of distress, and the development of depressive disorder during PEG-IFN-α-2a-based treatment. Nevertheless, this study was limited by a relatively small sample size, which may have affected our ability to detect depressive symptoms.

Despite the limitation, our results demonstrated that depressive disorder occurred in 22.4% of patients receiving PEG-IFN-α-2a during the early stage of antiviral treatment. All patients with HCV infection showed significant changes in fatigue, among other various depressive symptoms, during the course of IFN-based treatment. Those who developed MDD suffered higher levels of distress, indicating poor psychological well-being. Pretreatment BDI, BAI, and K-POMS scores were found to be useful predictors of IFN-induced depressive disorder. In light of our findings, we recommend that clinicians conduct a thoughtful psychological evaluation, addressing depression, anxiety, and somatic symptoms, as well as level of distress, before starting IFN-based treatment in patients with HCV infection. This may aid in improving psychological well-being and QOL, as well as compliance with IFN-based treatment.

Acknowledgments

We thank all the participants who gave us their time and support. This work was supported by a clinical research grant-in-aid from the Seoul Medical Center (03-2011-3).

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