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Interferon-alpha-induced depression: Comparisons between early- and late-onset subgroups and with patients with major depressive disorder

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ABSTRACT

Interferon (IFN)-alpha, until recently the standard treatment of hepatitis C virus (HCV) infection, is associated with a significant risk of major depressive episode (MDE, or IFN-alpha-induced depression). However, it is little studied the comparisons of clinical manifestations between IFN-alpha-induced depression and major depressive disorder (MDD). In addition, IFN-alpha induces different neuroinflammation and neuroendocrine status throughput the HCV treatment course; however, the clinical presentations have never been compared between early-onset and later-onset IFN-alpha-induced depression. We assessed 200 HCV patients starting IFN-alpha therapy bi-weekly for 24 weeks, with the structured interview for confirmation of diagnosis of IFN-alpha-induced depression and with clinical rating scales for depressive symptoms and neuropsychiatric symptoms. Subjects developed IFN-alpha-induced depression (n = 59, 30%) during the first 6 weeks of IFN-alpha therapy were defined as the early-onset group (n = 32), while those developed depression after the 6th week were defined as the late-onset group (n = 27). A matched group of MDD patients (n = 60) was used to compare specific clusters of depressive symptoms with early- and late-onset IFN-alpha-induced depression. Compared to the matched group of MDD patients, IFN-alpha-induced depression was significantly associated with more somatic symptoms and fewer symptoms of mood, anxiety and negative cognition. More somatic symptoms were also found in those who became clinically depressed at early stage of IFN-alpha therapy. We suggest that the specific somatic features of interferon-alpha-induced depression, and especially of early-onset depression, characterise individuals who are more sensitive to cytokines-induced changes in mood.

1. Introduction

Inflammation is increasingly recognized as contributing to the pathogenesis of depression, and the most strikingly supportive evidence for this inflammation theory is major depressive episode (MDE) induced by interferon (IFN)-alpha in patients with cancers or chronic viral infection (Chiu et al., 2017; Dantzer et al., 2008; Raison et al., 2006; Su, 2012). Chronic hepatitis C viral (HCV) infection is a major public health concern; however, the only standard treatment until recently, IFN-alpha in combination with ribavirin, is associated with significant risks of neuropsychiatric adverse effects. For example, up to 30% of patients develop IFN-alpha-induced depression (or major depressive episode according to DSM-IV diagnostic criteria) within the first 3 months (Schafer et al., 2007; Su et al., 2010; Udina et al., 2012). These neuropsychiatric side effects result in early discontinuation and poor outcome of IFN-α therapy (Dusheiko, 1997; Leutscher et al., 2010; Renault et al., 1987).

Substantiating the notion that IFN-alpha indeed induces major depression is that IFN-alpha-induced depression (Raison et al., 2006): (i) is responsive to standard antidepressant therapy (Capuron et al., 2002a; Farah, 2002; Musselman et al., 2001); (ii) is associated with alterations in monoamine metabolism and its metabolic enzyme, indoleamine 2,3, dioxygenase (IDO) (Capuron et al., 2002b; Raison et al., 2009; Raison et al., 2010b; Wichers et al., 2005b); (iii) is associated with alterations in hypothalamic-pituitaryadrenal (HPA) axis function (Capuron et al., 2003b; Raison et al., 2010a; Raison et al., 2010c); and (iv) can be effectively prevented by antidepressant agents, including specific serotonin reuptake inhibitors (Jiang et al., 2014) and omega-3 fatty acids

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(Su et al., 2014).

Clinically, it is interesting to know if there is any different clinical manifestation between the behavioral syndrome caused by innate immune cytokines and DSM-IV idiopathic major depressive disorder (MDD) in otherwise healthy individuals. Interestingly, in a previous study directly comparing symptom domains in patients with depression induced by IFN-alpha used for melanoma (n = 9) and in physically healthy patients with major depressive disorder (MDD) (n = 28), there were considerable overlaps for most of the clinical symptoms between the two groups. Patients with IFN-alpha-induced depression, however, had more motor retardation and weight loss, and less cognitive distortions, as compared with MDD patients (Capuron et al., 2009). While this study shedded some import light on the specific features of cytokine-induced depression, it was limited by the small sample size, and confounded by the higher IFN-alpha treatment dosage and the severe background disease of these patients, with malignant melanoma (Dieperink et al., 2000; Raison et al., 2005; Schaefer et al., 2002). Moreover, the depression rating scales were obtained at the time of maximum severity of depression rather than at the time of onset, thus making difficult to understand psychopathological differences between early-onset and later-onset IFN-alpha-induced depression, which may result from different sensitivity to cytokines and different molecular processes. Indeed, after the initial injection of IFN-alpha, almost all patients experience an acute sickness behaviour with flu-like symptoms and neuropsychiatric adverse effects induced by IFN-alpha (inflammation) (Capuron and Miller, 2004; Dieperink et al., 2000; Raison et al., 2005; Trask et al., 2000), which resemble the effects of cytokine administration in animals and the somatic/vegetative symptoms in major depressive disorder (Dantzer et al., 2008; Raison et al., 2006; Su, 2009). Interestingly, psychological complications, including low mood, suicidal ideation, negative thoughts and attentional deficits occurs more commonly in the following weeks to months (Asnis et al., 2006; Capuron et al., 2002a; Capuron et al., 2002b; Dieperink et al., 2000; Raison et al., 2005). However, this potential shitf in depressive symptomatology over the course of IFN-alpha has not been investigated in patients that anyway fulfil diagnostic criteria for major depression, albeit at different time-points in the course of the treatment.

To further explore the relationship between cytokines and depression, the aim of this study was to study the clinical phenotypes of n = 59 patients with IFN-alpha-induced major depression used for chronic viral hepatitis, a much less disabling condition, and requiring a smaller dose of IFN-alpha, when compared with malignant melanoma; and of n = 60 age- and gender-matched, physically healthy individuals with MDD. We specifically compared: 1) early-onset (before 6 weeks of treatment) and later-onset (after 6 weeks of treatment) IFN-alpha-induced depression; and 2) IFN-alpha-induced depression with MDD in physically-healthy individuals.

2. Materials and methods

2.1. Subject

Patients with chronic HCV were assessed for eligibility for IFN-alpha therapy by three hepatologists at the Liver Centre of the China Medical University Hospital, Taichung, Taiwan. Patients received combination therapy as their treatment for chronic HCV for 24 weeks (1.5 μg of peg-IFN alpha-2beta per kilogram of body weight subcutaneously once weekly, and 600–800 mg of ribavirin daily). Exclusion criteria included age over 70 years; prior IFN-alpha therapy; any autoimmune disorder; any cause for liver disease other than HCV; pregnancy; a lifetime history of mania, antisocial personality disorder, or psychotic disorders; current use of antidepressants, antipsychotics and mood stabilizers; and any current psychiatric disorder, suicidality, and substance abuse or dependence. HCV patients who developed MDE at any follow-up assessment during the 24-week therapy are definded as the “IFN-DEP” group, while HCV patients who did not develop MDE are definded as the “IFN-NON-DEP” group. In addition, the subjects developed IFN-alpha-induced depression at the assessments of the 2nd, 4th and 6th weeks of IFN-alpha therapy were defined as the Early IFN-DEP group, while those developed depression after the 6th week were defined as the Late IFN-DEP group. Sixty-three percent of the patients in this study were part of the samples previously published in our genetic association study (Su et al., 2010).

By matching sex and age to the IFN-DEP group, medically healthy individuals with major depressive disorder (definded as “MDD” group) were enrolled from the psychiatric outpatient clinic at the same hospital. Eligible patients who met the diagnostic criteria of DSM-IV for MDD were between 18 and 70 years old, physically healthy on medical history and physical examination and laboratory parameters within normal limits, and free from antipsychotics, antidepressant, and anticonvulsant medications for more than 2 weeks. Exclusion criteria included pregnancy; comorbidity of any suspected current Axis I disorders or suicidality; and any lifetime history of mania, antisocial personality disorder, or psychotic disorders. After complete explanation of the study to the subjects, written informed consents were obtained. The study was approved by the China Medical University Hospital Institutional Review Board. Data were collected from July 2008 to June 2011.

2.2. Experimental design

This was a 24-week, prospective, observerational study. Before starting the study, the hepatologists gave brief information to all volunteered HCV patients about this study and referred them to the researchers. The researchers then provided structured information about IFN-alpha-induced neuropsychiatric adverse effects and depression, and the procedure of this study. Patients had to fully understand and sign the informed consent before enrolment.

Patients were evaluated assessed bi-weekly for 24 weeks of IFN-alpha therapy. At each assessment, patients were assessed with the structured Mini International Neuropsychiatric Interview for DSM-IV Axis I Disorders (MINI) (Sheehan et al., 1998) for confirmation of diagnosis of MDE, with the 21-item Beck Depression Inventory (BDI) for depressive symptoms, and with the self-reported Neurotoxicity Rating Scale (NRS) (Valentine et al., 1995) and the Chalder Fatigue Questionnaire (Chalder et al., 1993) for other neuropsychiatric symptoms. Sociodemographic factors were recorded. Any adjunctive treatment was decided by treating physicians according to their clinical judgement and was not controlled by our study protocol.

For HCV patients who developed IFN-alpha-induced depression, the semi-structured version of 21-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) was applied to assess the severity of different clusters of depressive symptoms at the time when MDE diagnosis was made. The HDRS was also used in the matched group of MDD patients. The HRSD items were divided into the following clusters: *Core* (items 1, 2, 7, 8, 10, 13), *Sleep* (items 4, 5, 6), *Psychic Anxiety* (items 9, 10), *Somatic Anxiety* (items 11, 12, 13), and *Cognition* (items 2, 15, 20) (Serretti et al., 1998, 2007).

2.3. Psychometric measurements

The Mini-International Neuropsychiatric Interview (MINI) was applied for the detection new onset cases of major depressive episode during IFN-alpha therapy. MINI is a short structured diagnostic interview for psychiatric disorders according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) and the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). With an administration time of approximately 15 min, the MINI was designed to meet the need for a short but accurate structured psychiatric interview for multicenter clinical trials and epidemiology studies and to be used as a first step in outcome tracking in non-research clinical settings (Sheehan et al., 1998). The

information of translation, validation and instruction of Taiwanese version of MINI can be accessed on the website of Taiwanese Society of Psychiatry (http://www.sop.org.tw/dow_a.htm). This Taiwanese version had been shown a very good validation and inter-rater reliability after being retranslated into English, with the kappa value of 0.75, Z score value of 13.22 (Chou et al., 2007). The Taiwanese version of MINI has been used extensively, by us and others, in many clinical trials and epidemiology studies in Taiwan (Chou et al., 2007; Hsiao et al., 2002; Su et al., 2007; Su et al., 2010; Su et al., 2014; Teng et al., 2005).

The Depression Inventory (BDI) is a commonly used, self-administered, instrument in screening and severity-rating in depression (Beck et al., 1961). The second edition of BDI has been developed in 1996 to address all of the nine DSM-IV criteria for a major depressive episode (Beck et al., 1996). The second edition of BDI has been translated into multiple languages as well as Traditional Chinese in Taiwan, with a good validity and reliability of Cronbach's α of 0.94 (Lu et al., 2002).

The Neurotoxicity Rating Scale (NRS) is a checking-list questionnaire, with each item rated from 0 to 10 as a visual analogue scale, and is used for the evaluation of 39 neuropsychiatric symptoms related to cytokine therapy (Valentine et al., 1995). The developers, Professors Meyes and Valentine, did not develop any scoring system for the rating scale (personal communication), and used it only as an adverse effect checking list. In our study, we used the rating method of 0–10 for each item, like a visual analogue scale, as is suggested by the developer (personal communication). The NRS was translated into Traditional Chinese by the author, K.-P. Su, together with an American born Taiwanese nutritionist who is fluent in Chinese and English. The preliminary Traditional Chinese translation was then back-translated by the other two bilingual Taiwanese psychiatrists who are fluent in Chinese and English. Both of them were bicultural experts and were not given any information about the NRS. The back-translation was then discussed and reviewed by all researchers. We repeated the translation and back-translation procedures until complete agreement between English and Traditional Chinese versions was obtained.

The Chalder Fatigue Questionnaire (CFQ) has been developed and widely used both to measure the severity of fatigue and as an aid for assessing patients with Chronic Fatigue Syndrome (Chalder et al., 1993). The CFQ was translated into Traditional Chinese by the author, KP-Su, together with an American born Taiwanese nutritionist who is fluent in Chinese and English. The preliminary Traditional Chinese translation was then back-translated by the other two bilingual Taiwanese psychiatrists who are fluent in Chinese and English. Both of them were bicultural experts and were not given any information about the CFQ. The back-translation was then discussed and reviewed by all researchers. We repeated the translation and back-translation procedures until agreement between the English and Traditional Chinese versions was obtained.

2.4. Outcome measurement and statistic analysis

The independent-samples *t* or chi-square tests were used to compare continuous variables between IFN-DEP and IFN-NON-DEP groups. Logistic regression analysis was performed to find the predictors of the occurrence of IFN-alpha-induced depression. The effects of time (psychological measurements over times) and group (HCV patients with or without IFN-alpha-induced depression), as well as the time and group interaction, on the changes of BDI, NRS and CFQ scores were assessed with repeated measurement analyses in general linear modelling.

Univariate analysis of variance (ANOVA) was used to compare differences in HRSD symptoms among IFN-DEP, IFN-NON-DEP and MDD groups. The *post hoc* analyses for between-group comparisons were performed using Tukey test for pairwise comparisons. The "group" effect (IFN-DEP, IFN-NON-DEP and MDD groups) on HRSD symptoms was estimated with multivariate analysis of variance employing general linear modelling (MANOVA). Whenever appropriate, data were reported as Mean ± SD and the error bars were represented as standard error of the means (SEM) in the result figures. All data were analyzed using the SPSS version 15 statistical software (SPSS Inc., Chicago, Illinois, USA). *P* values < 0.05 were considered statistically significant.

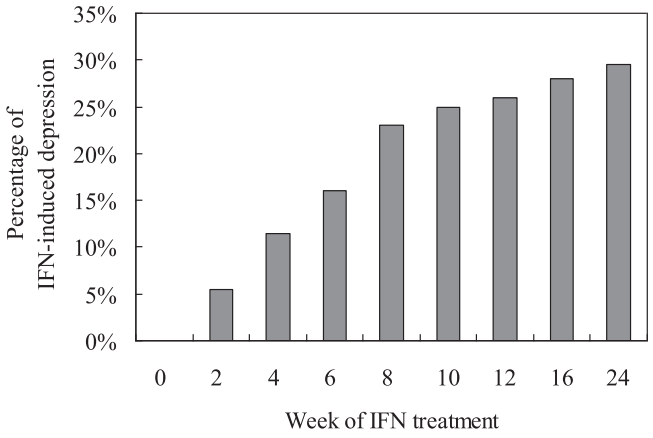

Fig. 1. The cumulative incidence rate of patients who developed IFN-alpha-induced depression at some point during 24-week treatment period.

3. Results

3.1. The incidence rate of IFN-alpha-induced depression

Two hundred and twenty-nine patients were referred. Thirteen from the 229 eligible patients who had current psychiatric disorders (5 with major depressive disorder and 8 with general anxiety disorder) were excluded. Sixteen withdrew consent or were lost in follow-up visits. Two hundred (87.3%) from 229 consent patients were completed the 24-week follow-up during IFN-alpha therapy. Men (n = 112) comprised 56% of the sample. Mean age was 50 years (SD, 11; range, 22–70 years). At baseline, no enrolled patient either met criteria for any current psychiatric disorder or took any psychotropic medication.

Fifty-nine patients developed IFN-alpha-induced depression (29.5%, IFN-DEP group) at any point during the 24-week therapy, while 141 patients did not develop IFN-alpha-induced depression (70.5%, IFN-NON-DEP group). Fig. 1 presents the cumulative percentages of patients that developed IFN-alpha-induced depression at the follow-up visits during IFN/ribavirin therapy. The numbers (percentages) of new cases of IFN-alpha-induced depression at weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 and 24, were 11 (5.5%), 12 (6%), 9 (4.5%), 14 (7%), 4 (2%), 2 (1%), 2 (1%), 2 (1%), 1 (0.5%), 1 (0.5%), 1 (0.5%) and 0 (0%), respectively.

3.2. Comparison of symptomatology among patients with IFN-alpha-induced depression before and after 6-week IFN-alpha therapy and patients with major depressive disorder

We compared clinical characteristics and symptom clusters of HDRS between the 3 groups from patients who developed IFN-alpha-induced depression within 6 weeks of IFN-alpha therapy (Early IFN-DEP group), or after 6 weeks (Late IFN-DEP group), or the gender- and age-matched patients with MDD. The HDRS scores and subscores of patients with IFN-induced depression were recorded at the time when MDE diagnosis was made. There were no significant differences in gender (chi-square = 1.3, p = 0.52) and age (p = 0.2) among the Early IFN-DEP group (n = 32 with 15 males), the Late IFN-DEP group (n = 27 with 11 males), and the matched MDD group (n = 60 with 25 males). In MANOVA analyses, there were significant effects of group ($F = 9.3$, $p < 0.001$) on expression of cluster symptoms in HRSD. Furthermore, the simple main effects and *post hoc* comparisons revealed group differences were significant in *Core* ($F = 10.6$, $p < 0.001$), *Psychic Anxiety* ($F = 16.5$, $p < 0.001$), *Somatic Anxiety* ($F = 23.8$, $p < 0.001$) and

Table 1
Mean ± SD scores of specific symptom clusters from the semi-structured version of 21-item Hamilton Depression Rating Scale (HDRS) in patients with early- versus late-onset IFN-alpha-induced depression and paitents with major depressive disorder (MDD).

	Early IFN-DEP (n = 32)	Late IFN-DEP (n = 27)	MDD (n = 60)
HDRS total scores	21.2 ± 3.5	21.8 ± 4.6	21.8 ± 4.3
HDRS symptom clusters			
Core (items 1, 2, 7, 8, 10, 13)	7.5 ± 1.8 **	8.5 ± 1.7	9.4 ± 2.0
Psychic anxiety (items 9, 10)	1.4 ± 1.2 **	1.9 ± 1.0 + +	2.9 ± 1.2
Cognition (items 2, 15, 20)	1.6 ± 1.0 *	1.8 ± 1.0	2.4 ± 1.2
Sleep (items 4, 5, 6)	3.9 ± 1.4	3.9 ± 1.6	3.6 ± 1.8
Somatic Anxiety (items 11, 12, 13)	5.9 ± 0.9 ** ^	4.9 ± 1.4	4.2 ± 1.2

Between groups comparisons with independent-samples *t* test results: *p < 0.01; **p < 0.001 for comparisons of MDD subjects to IFN-alpha-treated depressed subjects onset by the 6th week (Early IFN-DEP); + +p < 0.001 for for comparisons of MDD subjects to IFN-alpha-treated depressed subjects onset after the 6th week (Late IFN-DEP); ^p < 0.01 for comparisons of Early IFN-DEP to Late IFN-DEP Abbreviations SD = standard deviation IFN = interferon.

Cognition (F = 6.2, p = 0.003) symptom clusters, but not in total HDRS scores (F = 0.2, p = 0.78) or in the *Sleep* symptom cluster (F = 0.6, p = 0.53).

Table 1 presents the between-group comparisons for scores of specific symptom clusters between the Early IFN-DEP group, the Late IFN-DEP group, and the MDD group. Compared to the MDD patients, the Early IFN-DEP patients had more *Somatic Anxiety* and less *Core* symptoms, less *Psychic Anxiety*, and less *Cognition* symptom. In addition, the Early IFN-DEP patients had more *Somatic Anxiety* and a trend for less *Core* symptoms (p = 0.09), than the Late IFN-DEP patients. The Late IFN-DEP and MDD patients were not significantly different, except for less *Psychic Anxiety* in the Late IFN-DEP group.

We compared the demographic characteristics and baseline clinical manifestations between Early and Late IFN-DEP groups (not shown in the Tables). There were no significant differences between groups in gender distribution ($\chi 2 = 0.22$, p = 0.6), age (p = 0.09), education years (p = 0.7), marital status ($\chi 2 = 0.01$, p = 0.92) and history of major depression ($\chi 2 = 2.62$, p = 0.11). For baseline (before starting the IFN-alpha) depressive, fatigue, and neuropsychiatric symptoms, the Early IFN-DEP group had higher BDI (7.8 ± 7.5 vs. 3.8 ± 4.0, p < 0.001), but only slightly higher CFQ (9.7 ± 8.2 vs. 8.1 ± 9.8, p = 0.4) and NRS (45.9.7 ± 56.8 vs. 28.9 ± 41.1, p = 0.2), as compared with the Late IFN-DEP group.

Fig. 2 presents the mean (± SEM) scores of BDI (Fig. 2A), CFQ (Fig. 2B) and NRS (Fig. 2C) scores at weeks 0, 2, 4, 8, 12 and 24 of IFN-alpha therapy in Early and Late IFN-DEP and IFN-NON-DEP groups. Given the impact of early development of depressive and neuropsychiatric symptoms on IFN-alpha-induced depression, we compared the early changes in scores of BDI, NRS and CFQ between baseline and week 2. We found that those who later developed IFN-alpha-induced depression (either early or late onset) showed a greater increase in BDI (8.0 ± 9.2, or 145%), CFQ (5.9 ± 6.4, or 66%) and NRS (41.5 ± 39.0, or 108%) scores, while those who did not develop depression had no, or much smaller increases in BDI (0.4 ± 6.7, or 8.5%), CFQ (0.4 ± 6.0, or 5.9%) and NRS (2.7 ± 31.1, or 10%). The differences in these increases between IFN-DEP and IFN-NON-DEP groups are all significant (all p < 0.001). Interestingly, when comparing the early changes between Early and Late IFN-DEP groups, both groups showed increases in BDI (9.1 ± 8.8 and 7.0 ± 10.1), CFQ (6.8 ± 6.3 and 4.6 ± 6.6) and NRS (48.6 ± 45.0 and 30.6 ± 25.2) scores, but only the difference in NRS changes reached the significant level (p = 0.045).

4. Discussion

To our knowledge, this is the first study to compare clinical manifestations between early-onset and later-onset IFN-alpha-induced depression, and the largest such study comparing patients with IFN-alpha-induced depression and physically health individuals with 'psychiatric' MDD. We found that patients who develop IFN-alpha-induced depression before 6 weeks of IFN-alpha therapy have different phenotypes of depressive symptoms compared with both patients with later onset IFN-alpha-induced depression and patients with MDD. According to the results of Table 1, those who become clinically depressed at an early stage of IFN-alpha therapy have more somatic symptoms than those who become clinically depressed later and than patients with MDD. Furthermore, early-onset, but not late-onset, IFN-alpha-induced depression, is associated with less core depressive and cognitive symptoms than MDD.

Our findings are consistent with the only one previous small-scale study directly comparing symptom domains in malignant melanoma patients with IFN-alpha-induced depression (n = 9) to MDD (n = 28), in which they reported more motor retardation and less cognitive distortions in IFN-alpha-induced depression as compared to MDD (Capuron et al., 2009). We here demonstrate that these observations apply in particular to patients who develop IFN-alpha-induced depression early on, although interesting in this study the time of maximum depression occurred after an average of 7 ± 3 weeks of IFN-alpha treatment (Capuron et al., 2009), suggesting that all cases had an onset before week 6. The higher dose of IFN-alpha in the study by Capuron, due to its use for melanoma rather than for viral hepatitis, could explain this more rapid onset.

It has been proposed that the somatic symptoms might be "the outward manifestation of sensitization of the brain cytokine system that is normally activated in response to activation of the innate immune system and mediates the subjective, behavioural and physiological components of sickness (Dantzer, 2005)." Indeed, somatic symptoms in patients with or without depression are similar to the symptoms of "sickness behavior" induced by acute cytokine administration (Chang et al., 2017; Su, 2008, 2009, 2012), and may be underpinned by different biological mechanisms compared with more psychological and cognitive symptoms of depression. For example, we have previously shown that an inflammation-related genetic variation, the phospholipase A2 BanI GG genotype, is associated with more somatic symptoms of depression in both patients with IFN-alpha-induced depression and in physically-healthy patients with MDD (Chang et al., 2018; Su et al., 2010). In contrast to the acute inflammatory reaction, later stages of IFN-alpha administration is associated with a recovery of initial inflammatory reaction (Capuron et al., 2003a,b; Felger et al., 2007) and a development of tryptohan/monoamine dysregulation, which is particularly associated with the development of the more psychological and cognitive symptoms (Capuron et al., 2002b) such as low mood, suicidal ideation, negative thoughts and attentional deficits (Asnis et al., 2006; Capuron et al., 2002a,b; Dieperink et al., 2000; Raison et al., 2005). The findings from our present study imply that differential sensitivity to the inflammatory challenge, or to its downstream mediators like the tryptohan/monoamine dysregulation, may lead to the onset of depression in different people and at different stages; in particular, who develop early-onset depression seems to have a combination of more severe psychopathology before starting IFN-alpha (statistically significant for

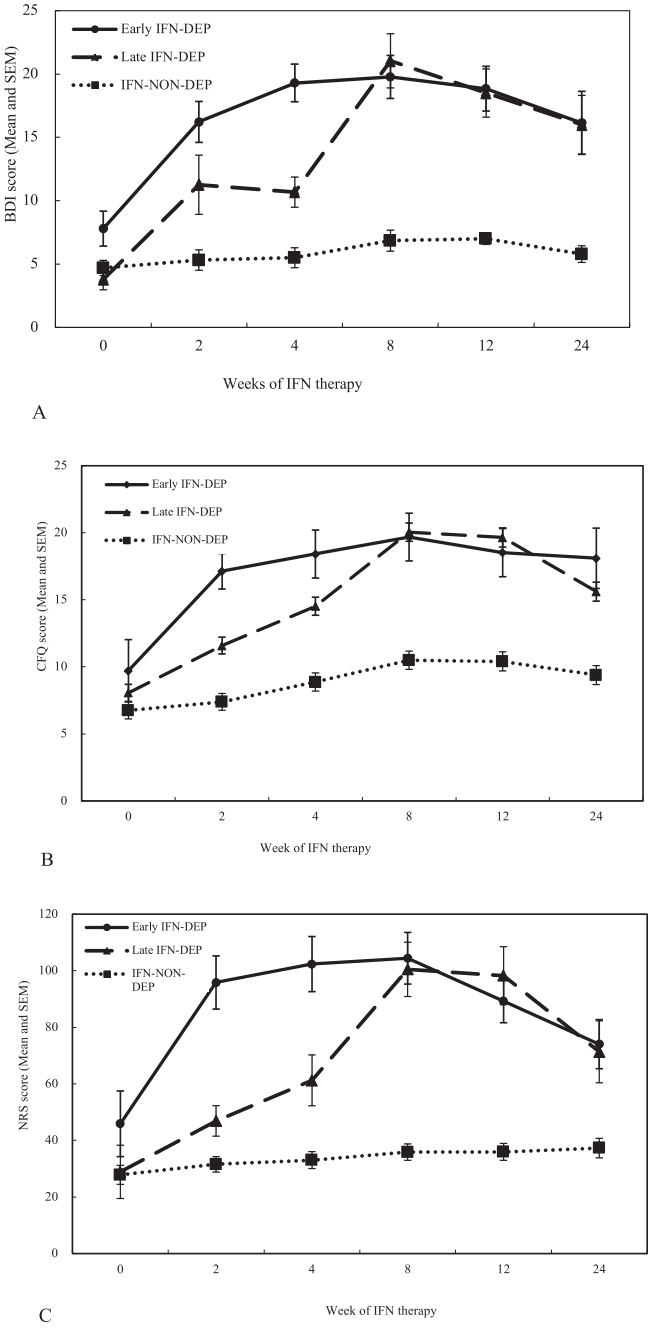

Fig. 2. Beck Depression Inventory (BDI, A), Chalder Fatigue Questionnaire (CFQ, B) and Neurotoxicity Rating Scale (NRS, C) and scores of patients without (n = 141) and with early- (n = 32) and late-onset (n = 27) IFN-alpha-induced depression during 24-week treatment period The mean ± standard error of the mean (SEM) scores of BDI, CFQ and NRS at weeks 0, 2, 4, 8, 12 and 24 of IFN-alpha therapy in groups of patients without (IFN-NON-DEP) and with early- (early IFN-DEP) and late-onset (late IFN-DEP) IFN-alpha-induced depression (IFN-NON-DEP).

BDI) and more severe increases in psychopathology during the first two weeks (statistically significant for NRF).

It has been reported that the development of depressive and neuropsychiatric symptoms in the early stage of IFN-alpha therapy can predict later development of major depression. For example, cancer patients who later developed IFN-alpha-induced depression displayed a higher increase in scores of the items of depressed mood, anorexia, fatigue and gastrointestinal symptoms at the first 2 weeks of IFN-alpha therapy (Capuron et al., 2002a; Whale et al., 2015). The impact of the early development of vegetative symptoms has been also reported in previous studies (Robaeys et al., 2007; Wichers et al., 2005a). In agreement with those results, our present study also found that the early increases in depressive (BDI), neuropsychiatric (NRS) and fatigue (CFQ) symptoms at the first 2 weeks predicted future onset of IFN-alpha-induced depression.

4.1. The incidence rate of IFN-alpha-induced depression in Taiwan

Although not the main aim of the study, it is worth commenting on the fact that this is the largest study examining the incidence of IFN-alpha-induced depression in a Han Chinese population. We found an incidence of 29.9%, a finding that is consistent with most prospective studies, in which the occurrence rates ranged from 20% to 45% (Beratis et al., 2005; Bonaccorso et al., 2002a,b; Constant et al., 2005; Hauser et al., 2002; Horikawa et al., 2003; Lotrich et al., 2007; Maddock et al., 2005; Miyaoka et al., 1999; Robaeys et al., 2007; Wichers et al., 2005a). In general, the diagnosis of major depressive episode from earlier studies was mostly based on non-structured interviews, resulting in higher occurrence rates from 41% to 45% (Bonaccorso et al., 2002a; Miyaoka et al., 1999). There were 2 studies using the structured interview, SCID, at lease once at month in the first three months. The incidence rates were 20% in the study with 60 patients of chronic hepatitis B and C (Maddock et al., 2004) and 39% in the other study with only 23 patients with chronic HCV (Lotrich et al., 2007). The MINI was applied as diagnostic tools by Wichers's group, reporting an occurrence rate of 31%. That study was, however, also limited by its very small sample size (n = 16) (Wichers et al., 2005a).

4.2. Limitations

There are methodological considerations and study limitations. *Firstly*, when using MINI as screening tool for major depressive episode, we focused on occurrence of major depressive episode during IFN-alpha therapy. Hence, the incidence of other IFN-alpha-induced psychiatric disorders, including manic episode and other psychotic disorders, was theoretically unknown. The patients, however, received regular clinical follow-up, and indeed we identified a patient who developed a manic episode (Wu et al., 2007). Therefore, we are confident that if psychotic or manic episodes had developed in the populations, we would have been alerted by the clinicians. *Secondly*, most of the patients with IFN-alpha-induced depression were detected quite early in the course of their depressive episode, usually by 2–4 weeks from onset; patients with MDD, however, had much longer duration of their clinical illness (mean = 17.4 weeks and SD = 13.2 weeks, not shown in the Results). The difference among groups might not be ruled out to be associated with the illness duration. *Thirdly*, there is no consensus to define the "early- and late-onset" IFN-alpha-induced depression or "early changes" of depression or other neuropsychiatric syndromes. In current study, we applied the cut-off point at week 6 for clinical diagnosis and week 2 for early syndromes mainly for practical considerations. As it takes 2 weeks with full syndrome to meet the diagnostic criteria, it might be proper to define as the development of early neuropsychiatric syndromes but it would be too early to define clinical MDE diagnosis at weeks 2 or 4. In addition, the cut-off point at week 6 makes the subgroups more even (n = 32 for early versus n = 27 for late) in current study, which could increase the statistic powers. *Fourthly*, due to the observational nature in design, this study is limited by the lack of control of adjunctive treatments. The clinicians prescribed all kind of adjunctive treatments very commonly, such as acetaminophen for headache and fever, antihistamines for nasal obstruction and rhinorrhea, benzodiazepines for insomnia and anxiety, antiemetic for nausea, loperamide and bismuth subsalicylate for diarrhea, erythropoetin for hemolytic anemia…etc. As the adjunctive treatments were widely distributed and closely associated with patients' condition and clinicians' decisions, we don't think it is proper to be controlled for the changes of

psychopathological changes or compared between groups in statistical adjustments in study analyses. *Finally*, the lack of reliability and validity tests of Taiwanese version of self-reported NRS and CFQ should be addressed as a methodology limitation in of our research.

In conclusion, IFN-alpha-induced depression, especially the early-onset subgroup, is associated with more somatic symptoms and less core depressive, anxious and cognitive symptoms, indicating that different biological mechanisms, and potential different sensitivity to an inflammatory challenge.

Conflict of interest

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References

Asnis, G.M., De La, G.R., 2006. Interferon-induced depression in chronic hepatitis C: a review of its prevalence, risk factors, biology, and treatment approaches. J. Clin. Gastroenterol. 40, 322–335.

Beck, A.T., Steer, R.A., Brown, G.K., 1996. Manual for the Beck Depression Inventory-II. Psychological Corporation, San Antonio, Texas.

Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., Erbaugh, J., 1961. An inventory for measuring depression. Arch. Gen. Psychiatry 4, 561–571.

Beratis, S., Katrivanou, A., Georgiou, S., Monastirli, A., Pasmatzi, E., Gourzis, P., et al., 2005. Major depression and risk of depressive symptomatology associated with short-term and low-dose interferon-alpha treatment. J. Psychosom. Res. 58, 15–18.

Bonaccorso, S., Marino, V., Biondi, M., Grimaldi, F., Ippoliti, F., Maes, M., 2002a. Depression induced by treatment with interferon-alpha in patients affected by hepatitis C virus. J. Affect. Disord. 72, 237–241.

Bonaccorso, S., Marino, V., Puzella, A., Pasquini, M., Biondi, M., Artini, M., et al., 2002b. Increased depressive ratings in patients with hepatitis C receiving interferon-alpha-based immunotherapy are related to interferon-alpha-induced changes in the serotonergic system. J. Clin. Psychopharmacol. 22, 86–90.

Capuron, L., Fornwalt, F.B., Knight, B.T., Harvey, P.D., Ninan, P.T., Miller, A.H., 2009. Does cytokine-induced depression differ from idiopathic major depression in medically healthy individuals? J Affect Disord. 119, 181–185.

Capuron, L., Gumnick, J.F., Musselman, D.L., Lawson, D.H., Reemsnyder, A., Nemeroff, C.B., et al., 2002a. Neurobehavioral effects of interferon-alpha in cancer patients: phenomenology and paroxetine responsiveness of symptom dimensions. Neuropsychopharmacology 26, 643–652.

Capuron, L., Miller, A.H., 2004. Cytokines and psychopathology: lessons from interferon-alpha. Biol. Psychiatry 56, 819–824.

Capuron, L., Neurauter, G., Musselman, D.L., Lawson, D.H., Nemeroff, C.B., Fuchs, D., et al., 2003a. Interferon-alpha-induced changes in tryptophan metabolism. relationship to depression and paroxetine treatment. Biol. Psychiatry 54, 906–914.

Capuron, L., Raison, C.L., Musselman, D.L., Lawson, D.H., Nemeroff, C.B., Miller, A.H., 2003b. Association of exaggerated HPA axis response to the initial injection of interferon-alpha with development of depression during interferon-alpha therapy. Am. J. Psychiatry 160, 1342–1345.

Capuron, L., Ravaud, A., Neveu, P.J., Miller, A.H., Maes, M., Dantzer, R., 2002b. Association between decreased serum tryptophan concentrations and depressive symptoms in cancer patients undergoing cytokine therapy. Mol. Psychiatry 7, 468–473.

Chalder, T., Berelowitz, G., Pawlikowska, T., Watts, L., Wessely, S., Wright, D., et al., 1993. Development of a fatigue scale. J. Psychosom. Res. 37, 147–153.

Chang, J.P., Guu, T.W., Chen, Y.C., Galecki, P., Walczewska, A., Su, K.P., 2018. BanI polymorphism of cytosolic phospholipase A2 gene and somatic symptoms in medication-free acute depressed patients. Prostaglandins Leukot Essent Fatty Acids 136, 111–115.

Chang, J.P., Lai, H.C., Yang, H.T., Su, W.P., Peng, C.Y., Galecki, P., et al., 2017. Polyunsaturated fatty acids levels and initial presentation of somatic symptoms induced by interferon-alpha therapy in patients with chronic hepatitis C viral infection. Nutr. Neurosci. 20, 291–296.

Chiu, W.C., Su, Y.P., Su, K.P., Chen, P.C., 2017. Recurrence of depressive disorders after interferon-induced depression. Transl Psychiatry 7, e1026.

Chou, F.H., Wu, H.C., Chou, P., Su, C.Y., Tsai, K.Y., Chao, S.S., et al., 2007. Epidemiologic psychiatric studies on post-disaster impact among Chi-Chi earthquake survivors in Yu-Chi Taiwan. Psychiatry Clin. Neurosci. 61, 370–378.

Constant, A., Castera, L., Dantzer, R., Couzigou, P., de Ledinghen, V., Demotes-Mainard, J., et al., 2005. Mood alterations during interferon-alfa therapy in patients with chronic hepatitis C: evidence for an overlap between manic/hypomanic and depressive symptoms. J Clin. Psychiatry 66, 1050–1057.

Dantzer, R., 2005. Somatization: a psychoneuroimmune perspective. Psychoneuroendocrinology 30, 947–952.

Dantzer, R., O'Connor, J.C., Freund, G.G., Johnson, R.W., Kelley, K.W., 2008. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat. Rev. Neurosci. 9, 46–56.

Dieperink, E., Willenbring, M., Ho, S.B., 2000. Neuropsychiatric symptoms associated with hepatitis C and interferon alpha: a review. Am. J. Psychiatry 157, 867–876.

Dusheiko, G., 1997. Side effects of alpha interferon in chronic hepatitis C. Hepatology 26, 112S–121S.

Farah, A., 2002. Interferon-induced depression treated with citalopram. J. Clin Psychiatry 63, 166–167.

Felger, J.C., Alagbe, O., Hu, F., Mook, D., Freeman, A.A., Sanchez, M.M., et al., 2007. Effects of Interferon-alpha on rhesus monkeys: a nonhuman primate model of cytokine-induced depression. Biol. Psychiatry 62, 1324–1333.

Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56–62.

Hauser, P., Khosla, J., Aurora, H., Laurin, J., Kling, M.A., Hill, J., et al., 2002. A prospective study of the incidence and open-label treatment of interferon-induced major depressive disorder in patients with hepatitis C. Mol. Psychiatry 7, 942–947.

Horikawa, N., Yamazaki, T., Izumi, N., Uchihara, M., 2003. Incidence and clinical course of major depression in patients with chronic hepatitis type C undergoing interferon-alpha therapy: a prospective study. Gen. Hosp. Psychiatry 25, 34–38.

Hsiao, M.C., Liu, C.Y., Chen, K.C., Hsieh, T.T., 2002. Characteristics of women seeking treatment for premenstrual syndrome in Taiwan. Acta Psychiatr. Scand. 106, 150–155.

Jiang, H.Y., Deng, M., Zhang, Y.H., Chen, H.Z., Chen, Q., Ruan, B., 2014. Specific serotonin reuptake inhibitors prevent interferon-alpha-induced depression in patients with hepatitis C: a meta-analysis. Clin. Gastroenterol. Hepatol. 12 (1452–60), e3.

Leutscher, P.D., Lagging, M., Buhl, M.R., Pedersen, C., Norkrans, G., Langeland, N., et al., 2010. Evaluation of depression as a risk factor for treatment failure in chronic hepatitis C. Hepatology 52, 430–435.

Lotrich, F.E., Rabinovitz, M., Gironda, P., Pollock, B.G., 2007. Depression following pegylated interferon-alpha: characteristics and vulnerability. J. Psychosom. Res. 63, 131–135.

Lu, M.L., Che, H.H., Chang, S.W., Shen, W.W., 2002. Reliability and validity of the Chinese version of the Beck Depression Inventory-II. Taiwanese J. Psychiatry 16, 301–310.

Maddock, C., Baita, A., Orru, M.G., Sitzia, R., Costa, A., Muntoni, E., et al., 2004. Psychopharmacological treatment of depression, anxiety, irritability and insomnia in patients receiving interferon-alpha: a prospective case series and a discussion of biological mechanisms. J. Psychopharmacol. 18, 41–46.

Maddock, C., Landau, S., Barry, K., Maulayah, P., Hotopf, M., Cleare, A.J., et al., 2005. Psychopathological symptoms during interferon-alpha and ribavirin treatment: effects on virologic response. Mol. Psychiatry 10, 332–333.

Miyaoka, H., Otsubo, T., Kamijima, K., Ishii, M., Onuki, M., Mitamura, K., 1999. Depression from interferon therapy in patients with hepatitis C. Am. J. Psychiatry 156, 1120.

Musselman, D.L., Lawson, D.H., Gumnick, J.F., Manatunga, A.K., Penna, S., Goodkin, R.S., et al., 2001. Paroxetine for the prevention of depression induced by high-dose interferon alfa. N. Engl. J. Med. 344, 961–966.

Raison, C.L., Borisov, A.S., Majer, M., Drake, D.F., Pagnoni, G., Woolwine, B.J., et al., 2009. Activation of central nervous system inflammatory pathways by interferon-alpha: relationship to monoamines and depression. Biol. Psychiatry 65, 296–303.

Raison, C.L., Borisov, A.S., Woolwine, B.J., Massung, B., Vogt, G., Miller, A.H., 2010a. Interferon-alpha effects on diurnal hypothalamic-pituitary-adrenal axis activity: relationship with proinflammatory cytokines and behavior. Mol. Psychiatry 15, 535–547.

Raison, C.L., Capuron, L., Miller, A.H., 2006. Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol. 27, 24–31.

Raison, C.L., Dantzer, R., Kelley, K.W., Lawson, M.A., Woolwine, B.J., Vogt, G., et al., 2010b. CSF concentrations of brain tryptophan and kynurenines during immune stimulation with IFN-alpha: relationship to CNS immune responses and depression. Mol. Psychiatry 15, 393–403.

Raison, C.L., Demetrashvili, M., Capuron, L., Miller, A.H., 2005. Neuropsychiatric adverse effects of interferon-alpha: recognition and management. *CNS*. Drugs 19, 105–123.

Raison, C.L., Rye, D.B., Woolwine, B.J., Vogt, G.J., Bautista, B.M., Spivey, J.R., et al., 2010c. Chronic interferon-alpha administration disrupts sleep continuity and depth in patients with hepatitis C: association with fatigue, motor slowing, and increased evening cortisol. Biol. Psychiatry 68, 942–949.

Renault, P.F., Hoofnagle, J.H., Park, Y., Mullen, K.D., Peters, M., Jones, D.B., et al., 1987. Psychiatric complications of long-term interferon alfa therapy. Arch. Intern. Med. 147, 1577–1580.

Robaeys, G., De, B.J., Wichers, M.C., Bruckers, L., Nevens, F., Michielsen, P., et al., 2007. Early prediction of major depression in chronic hepatitis C patients during peg-interferon alpha-2b treatment by assessment of vegetative-depressive symptoms after four weeks. World J. Gastroenterol. 13, 5736–5740.

Schaefer, M., Engelbrecht, M.A., Gut, O., Fiebich, B.L., Bauer, J., Schmidt, F., et al., 2002. Interferon alpha (IFNalpha) and psychiatric syndromes: a review. Prog. Neuropsychopharmacol. Biol. Psychiatry 26, 731–746.

Schafer, A., Wittchen, H.U., Seufert, J., Kraus, M.R., 2007. Methodological approaches in the assessment of interferon-alfa-induced depression in patients with chronic hepatitis C - a critical review. Int. J. Methods Psychiatr. Res. 16, 186–201.

Serretti, A., Lattuada, E., Cusin, C., Macciardi, F., Smeraldi, E., 1998. Analysis of depressive symptomatology in mood disorders. Depress. Anxiety 8, 80–85.

Serretti, A., Mandelli, L., Lorenzi, C., Pirovano, A., Olgiati, P., Colombo, C., et al., 2007. Serotonin transporter gene influences the time course of improvement of “core” depressive and somatic anxiety symptoms during treatment with SSRIs for recurrent mood disorders. Psychiatry Res. 149, 185–193.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., et al., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin. Psychiatry 20 (59 Suppl.), 22–33.

Su, K.P., 2008. Mind-body interface: the role of n-3 fatty acids in psychoneuroimmunology, somatic presentation, and medical illness comorbidity of depression. Asia Pac. J. Clin. Nutr. 17 (Suppl. 1), 151–157.

Su, K.P., 2009. Biological mechanism of antidepressant effect of omega-3 fatty acids: how does fish oil act as a 'Mind-body interface'? Neurosignals 17, 144–152.

Su, K.P., 2012. Inflammation in psychopathology of depression: clinical, biological, and therapeutic implications. BioMedicine 2, 68–74.

Su, K.P., Chiu, T.H., Huang, C.L., Ho, M., Lee, C.C., Wu, P.L., et al., 2007. Different cutoff points for different trimesters? The use of Edinburgh Postnatal Depression Scale and Beck Depression Inventory to screen for depression in pregnant Taiwanese women. Gen. Hosp. Psychiatry 29, 436–441.

Su, K.P., Huang, S.Y., Peng, C.Y., Lai, H.C., Huang, C.L., Chen, Y.C., et al., 2010. Phospholipase A2 and Cyclooxygenase 2 Genes Influence the Risk of Interferon-alpha-Induced depression by regulating polyunsaturated fatty acids levels. Biol. Psychiatry 67, 550–557.

Su, K.P., Lai, H.C., Yang, H.T., Su, W.P., Peng, C.Y., Chang, J.P., et al., 2014. Omega-3 fatty acids in the prevention of interferon-alpha-induced depression: results from a randomized, controlled trial. Biol. Psychiatry 76, 559–566.

Teng, H.W., Hsu, C.S., Shih, S.M., Lu, M.L., Pan, J.J., Shen, W.W., 2005. Screening postpartum depression with the Taiwanese version of the Edinburgh Postnatal Depression scale. Compr. Psychiatry 46, 261–265.

Trask, P.C., Esper, P., Riba, M., Redman, B., 2000. Psychiatric side effects of interferon therapy: prevalence, proposed mechanisms, and future directions. J. Clin. Oncol. 18, 2316–2326.

Udina, M., Castellvi, P., Moreno-Espana, J., Navines, R., Valdes, M., Forns, X., et al., 2012. Interferon-induced depression in chronic hepatitis C: a systematic review and meta-analysis. J. Clin. Psychiatry 73, 1128–1138.

Valentine, A.D., Meyers, C.A., Talpaz, M., 1995. Treatment of neurotoxic side effects of interferon-alpha with naltrexone. Cancer Invest. 13, 561–566.

Whale, R., Fialho, R., Rolt, M., Eccles, J., Pereira, M., Keller, M., et al., 2015. Psychomotor retardation and vulnerability to interferon alpha induced major depressive disorder: Prospective study of a chronic hepatitis C cohort. J Psychosom Res 79, 640–645.

Wichers, M.C., Koek, G.H., Robaeys, G., Praamstra, A.J., Maes, M., 2005a. Early increase in vegetative symptoms predicts IFN-alpha-induced cognitive-depressive changes. Psychol. Med. 35, 433–441.

Wichers, M.C., Koek, G.H., Robaeys, G., Verkerk, R., Scharpe, S., Maes, M., 2005b. IDO and interferon-alpha-induced depressive symptoms: a shift in hypothesis from tryptophan depletion to neurotoxicity. Mol. Psychiatry 10, 538–544.

Wu, P.L., Liao, K.F., Peng, C.Y., Pariante, C.M., Su, K.P., 2007. Manic episode associated with citalopram therapy for interferon-induced depression in a patient with chronic hepatitis C infection. Gen. Hosp. Psychiatry 29, 374–376.