Original article

Biphasic pattern of depression and its predictors during pegylated interferon-based therapy in chronic hepatitis B and C patients

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Background: It remains unclear whether depression in chronic hepatitis B (CHB) and chronic hepatitis C (CHC) during pegylated interferon-based therapy is associated with the virus, drug or ethnic background. We aimed to perform a prospective study to evaluate the clinical course of depression and its predictors in consecutive non-cirrhotic CHB and CHC patients of the same ethnicity receiving pegylated interferon-based therapy.

Methods: The occurrence and severity of depression were actively assessed by the Hamilton Depression Rating Scale before therapy and at weeks 2, 4, 6, 8, 10, 12 and every 4 weeks during treatment until the end of therapy. Extensive numbers of variables (repeated measurements, time variables and interactions between all variables) were included in generalized estimating equations to analyse the predictors of depression.

Results: A total of 158 consecutive patients (73 CHB and 85 CHC patients) were enrolled. Depression (Hamilton Depression Rating Scale ≥11) occurred in a biphasic pattern at treatment weeks 2–10 and weeks 16–36. Treatment weeks <10 predicts more depression, and treatment weeks >12 predicts less depression, suggesting the predictability of the time variable during treatment on depression. Furthermore, CHC or pre-existing depression is an independent predictor of depression in these patients (P<0.001).

Conclusions: Depression occurred in a biphasic pattern during pegylated interferon-based therapy and should be early and actively assessed, especially in patients with CHC or pre-existing depression.

Introduction

HBV and HCV infections are a global health problem. Both lead to acute and chronic hepatitis, cirrhosis and hepatocellular carcinoma. HBV infects more than 350 million individuals and HCV 170 million people worldwide [1–3]. In the United States, 1.2 million individuals have chronic HBV infection and 2.7 million have active HCV infection [2,4].

Pegylated interferon (PEG-IFN) therapy has been approved in the treatment of chronic hepatitis B (CHB). A combination of PEG-IFN and ribavirin is the backbone of current standard treatment for chronic hepatitis C (CHC). During PEG-IFN and ribavirin treatment in CHC, depression is one of the causes of impaired health-related quality of life and treatment failure [5,6]. Depression has also been associated with poorer treatment response independent of dose reduction [7,8]. PEG-IFN and ribavirin treatment may also lead to suicidal behaviour that must be prevented [9–11].

Pre-existing depression before initiation of therapy was a risk factor for depression during treatment [6,12,13], which is also a risk for on-treatment poor compliance [14]. History of major depression is also a predictive factor, but only through the association with increased baseline depression status [15]. Thus,
psychological assessment before treatment initiation is important.

Besides initial depression status, an important step to prevent and effectively manage depression is to determine its predictors at baseline and during the clinical course of PEG-IFN-based therapy. Two studies [16,17] interestingly showed more frequent depression in CHC than CHB patients during IFN-based therapy. It remains unclear whether depression in chronic hepatitis is associated with the virus, the drug or the ethnic background [18]. The aim of this study is to evaluate prospectively the clinical course of depression and the risk factors associated with the development of depression in both CHB and CHC patients of the same ethnicity receiving PEG-IFN-based therapy.

Methods

We performed a prospective cohort study to actively evaluate the frequency and severity of depression in consecutive, non-cirrhotic patients with CHB or CHC who were treated with PEG-IFN-based therapy for active hepatitis in Cathay General Hospital Medical Center, Taipei, Taiwan. Active hepatitis was defined as increased alanine aminotransferase to more than 2× the upper limit of normal and/or histological evidence of liver inflammation or fibrosis. CHB was defined as a carrier of hepatitis B surface antigen (HBsAg) for at least 6 months before enrolment. CHC was defined as an individual with positive anti-HCV for at least 6 months before enrolment. Sustained virological response was defined as undetectable viral load at 6 months after treatment cessation in both CHB and CHC patients. Patients with coinfection of two viral hepatitis infections, HIV infection, alcohol abuse (>50 g/day), intravenous drug use, drug hepatitis, autoimmune hepatitis, metabolic liver disease or post-transplantation status were excluded. The institutional review board approved the study. After complete description of the study to the patients, written informed consent was obtained.

National Health Insurance (NHI) reimbursed treatment of CHB and CHC in Taiwan. The treatment regimen and duration according to the NHI criteria were as follows: hepatitis B e antigen (HBeAg)-positive CHB patients received once-weekly injections of 180 µg of PEG-IFN-α2a (Pegasys; F Hoffmann-La Roche Ltd., Basel, Switzerland) for 24 weeks and HBeAg-negative patients received 48 weeks of treatment. CHC patients received once-weekly injections of 180 µg of PEG-IFN-α2a or 1.5 µg/kg of PEG-IFN-α2b (Peg-Intron; Schering-Plough Co., Imishannon, County Cork, Ireland), plus daily 800–1,200 mg of ribavirin for 24 weeks of treatment, irrespective of viral genotype or viral load. Dose modification and discontinuation of PEG-IFN or ribavirin were determined according to the manufacturers’ guidelines. Patients were treated by three physicians (A, B and C); of them, 76% by physician A.

Assessment of depression

The occurrence and severity of depression was actively assessed by the Hamilton Depression Rating Scale (HAM-D) [19], one of the most commonly used scales for rating depression in medical research. This questionnaire consists of 17 questions, each has 3–5 possible responses with their corresponding scores. The general guidelines for the total score are: less than or equal to 7= normal, 8–10= borderline, 11–13= mild depression, 14–17= moderate depression, more than or equal to 18= severe depression. A structured interview guide for the scale is available [20]. The interview was performed by either one of two well-trained nurses. Patients were assessed just before the initiation of PEG-IFN-based therapy and at weeks 2, 4, 6, 8, 10, 12 and every 4 weeks during treatment until the end of 24 or 48 weeks of therapy. Patients with HAM-D of more than or equal to 8 were given 50 mg of sertraline daily (Zoloft; Pfizer Australia Pty Limited, West Ryde, NSW, Australia) until either the end of treatment or symptoms relieved completely. Patients with severe depression despite sertraline therapy were discontinued from treatment.

Serological and virological assays

Serum HBsAg and HBeAg were tested by Ausria-II and IMx HBe 2.0 (Abbott Laboratories, North Chicago, IL, USA), respectively. Serum anti-HCV was assayed by Murex anti-HCV (Murex Biotech, Kyalami, South Africa).

We used an in-house real-time PCR assay for quantification of HBV DNA, as previously described [21]. The detection limit of this assay was 5×10² copies/ml. The HCV RNA level was performed by reverse-transcription PCR using ABI Prism 7000 Sequence Detection System (Applied Biosystems, Foster City, CA, USA) and genotyping was performed with type-specific primers [22]. The detection limit of HCV RNA was 500 IU/ml.

Statistical analyses

Characteristics at baseline and on treatment were compared among study groups. Continuous variables were evaluated by Student’s t-test. Categorical variables were expressed as frequencies with proportions and compared using Pearson’s χ² test. The HAM-D score at each treatment time point was compared by Mann–Whitney U test. All of the tests were two-tailed and a P-value <0.05 was considered statistically significant.

Generalized estimating equations (GEE) were applied for predictors of depression (HAM-D score) in all (CHB plus CHC) patients. We also analysed predictors of depression in each group of patients (CHB or CHC) separately. The missing values in the
HAM-D score during separate analysis of predictors in CHB or CHC patients were overcome by using multiple imputations [23–25]. A total of five imputation datasets were generated. Every data set was fitted into a regression model. The five regression models were then combined.

Results

Patient characteristics

A total of 158 consecutive patients treated with PEG-IFN-based therapy (73 CHB and 85 CHC) were recruited from the outpatient clinic of Cathay General Hospital Medical Center. Characteristics of these patients are shown in Table 1. Male gender was more predominant in CHB than CHC patients (85% versus 51%; \( P < 0.001 \)). The mean age of CHB patients was younger than that of CHC (41 versus 54 years; \( P < 0.001 \)). Among them, 3 of 36 HBeAg-positive CHB patients received an additional 24 weeks self-paid treatment after 24 weeks of NHIC reimbursed therapy. Among the 37 HBeAg-negative CHB patients, 31 were treated for 48 weeks by NHIC reimbursement, 5 received self-paid treatment for 24 weeks and 1 patient discontinued the treatment because of severe depression. Among the CHC patients, 63 were treated for 24 weeks by NHIC reimbursement, 18 received an additional 24 weeks self-paid treatment and 4 discontinued treatment because of the following reasons: 1 because of thrombocytopenia, 1 because of urosepsis, 1 died as a result of sepsis and another 1 died of a non-liver related cause. Baseline mean haemoglobin was higher in CHB than CHC patients (14.5 versus 13.7 g/dl; \( P = 0.001 \)). Median baseline HAM-D score was higher in CHB than CHC patients (14.5 versus 9.0; \( P = 0.001 \)). During treatment, haemoglobin of less than 10 g/dl was observed in more CHC than CHB patients (28% versus 4%; \( P < 0.001 \)) as expected because of the combination of ribavirin in CHC patients with more resultant erythropoietin use in CHC patients (36.5% versus 0%; \( P < 0.001 \)). 

Clinical course of depression and its predictors

Depression (HAM-D score ≥11) occurred in a biphasic pattern, at treatment weeks 2–10 and weeks 16–36 (Figure 1). Depression was detected in more CHB than CHC patients during PEG-IFN-based therapy (Figure 1). HAM-D score was higher in CHC than CHB patients at baseline \( (P = 0.032; \) Table 1) and during treatment from week

### Table 1. Characteristics of consecutive patients with CHB and CHC treated with pegylated interferon-based therapy

<table>
<thead>
<tr>
<th>Variables</th>
<th>CHB</th>
<th>CHC</th>
<th>( P )-value</th>
</tr>
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<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients, n</td>
<td>73</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>62 (85)</td>
<td>43 (51)</td>
<td>(&lt; 0.001^a)</td>
</tr>
<tr>
<td>Mean age, years ± sd</td>
<td>41 ± 11</td>
<td>54 ± 11</td>
<td>(&lt; 0.001^a)</td>
</tr>
<tr>
<td>Mean ALT, IU/ml ± sd</td>
<td>11.49 ± 7.77</td>
<td>12.26 ± 8.85</td>
<td>0.417^b</td>
</tr>
<tr>
<td>Positive HBeAg, n (%)</td>
<td>36 (49)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Median HBV DNA, log10 IU/ml (range)</td>
<td>5.14 (1.38–8.36)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Median HCV RNA, log10 IU/ml (range)</td>
<td>NA</td>
<td>5.29 (2.34–7.31)</td>
<td></td>
</tr>
<tr>
<td>Physician A, n (%)</td>
<td>59 (79)</td>
<td>61 (72)</td>
<td>0.184^c</td>
</tr>
<tr>
<td>Mean haemoglobin, g/dl ± sd</td>
<td>14.5 ± 1.5</td>
<td>13.7 ± 1.5</td>
<td>0.002^c</td>
</tr>
<tr>
<td>Mean ALT, IU/l ± sd</td>
<td>1.52 ± 1.41</td>
<td>1.52 ± 1.41</td>
<td>0.032^d</td>
</tr>
<tr>
<td>Median HAM-D[an], n (range)</td>
<td>56 (0–8)</td>
<td>65 (2–8)</td>
<td>0.032^d</td>
</tr>
<tr>
<td>During treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment duration [24/48 weeks], n</td>
<td>38 (34)</td>
<td>63 (38)</td>
<td>0.001^e</td>
</tr>
<tr>
<td>Sertraline use, n (%)</td>
<td>10 (33.3)</td>
<td>16 (44.4)</td>
<td>0.386^e</td>
</tr>
<tr>
<td>Haemoglobin &lt;10 g/dl, n (%)</td>
<td>3 (4)</td>
<td>24 (28)</td>
<td>(&lt; 0.001^e)</td>
</tr>
<tr>
<td>Erythropoietin use, n (%)</td>
<td>0 (0)</td>
<td>31 (36.5)</td>
<td>(&lt; 0.001^e)</td>
</tr>
<tr>
<td>After treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sustained virological response, n (%)</td>
<td>8 (11)</td>
<td>45 (53)</td>
<td>(&lt; 0.001^e)</td>
</tr>
</tbody>
</table>

*a Pearson's \( \chi^2 \); b Student's t-test; c All patients were treated by three physicians (A, B and C), mostly by physician A; d Mann–Whitney U test. e One chronic hepatitis B (CHB) patient discontinued treatment as a result of depression. f One chronic hepatitis C (CHC) patient discontinued treatment as a result of thrombocytopenia, one patient as a result of urosepsis and two patients died (one as a result of sepsis and one as a result of non-liver related cause). ALT, alanine aminotransferase; HAM-D, Hamilton Depression Rating Scale available number (score 0–17); HBeAg, hepatitis B e antigen; NA, not applicable.
2 to week 20 ($P<0.05$ for each time point; Figure 2). We generated a GEE model for predictors of depression (HAM-D score) in both CHB and CHC patients. Table 2 included the variables with a $P$-value of less than 0.05 ($r^2 = 0.151$).

CHC is an independent predictor of more depression during PEG-IFN-based therapy ($P<0.001$). Baseline depression also predicts more depression during treatment period ($P<0.001$). Treatment week 24 predicts less depression in male patients ($P=0.018$).

**Figure 1.** Biphasic pattern of depression during pegylated interferon-based therapy in CHB and CHC patients

Number of chronic hepatitis B (CHB) and chronic hepatitis C (CHC) patients with depression (Hamilton Depression Rating Scale (HAM-D score) of ≥11) before and at each time point (treatment week) of pegylated interferon-based therapy. One patient might be included in more than one bar.

**Figure 2.** HAM-D before and during pegylated interferon-based therapy in CHB and CHC patients

Hamilton Depression Rating Scale (HAM-D; mean ±sd) among chronic hepatitis B (CHB) and chronic hepatitis C (CHC) patients before and at each time point (treatment week) of pegylated interferon-based therapy. Mann–Whitney U test was used to compare HAM-D score among the two groups at each time point.
Predictors of depression in CHC patients
We also generated a GEE model for predictors of depression (HAM-D score) in CHC patients. The variables with a P-value of less than 0.05 were included in Additional file 1 ($r^2 0.215$). Age was grouped by the cutoff of 60 years old based on a smoothing plot (Additional file 1). Baseline depression predicts more depression along treatment period ($P<0.001$). Sertraline use correlates with more depression because of indication of its use in patients with depression ($P=0.02$). Serum haemoglobin level also correlates with more depression ($P=0.017$). Treatment at week 16 predicts less depression in male CHC patients ($P=0.047$). Treatment weeks 4 and 6 predicts more depression in CHC patients older than 60 years ($P=0.005$ and $P=0.006$, respectively).

Predictors of depression in CHB patients
We also generated a GEE model for predictors of depression (HAM-D score) in CHB patients. The variables with a P-value of less than 0.05 were included in Additional file 1 ($r^2 0.189$). Age was grouped by the cutoff of 40 and 55 years old based on a smoothing plot (Additional file 1). Treatment duration of more than 48 weeks, in comparison with less than 48 weeks, predicts more depression along treatment period ($P=0.028$). Baseline logarithm of serum HBV DNA level predicts less depression ($P=0.003$); furthermore, HBV DNA level at treatment week 24 also predicts less depression ($P=0.032$). HBeAg positivity predicts more depression ($P<0.001$); however, the HBeAg positivity at treatment week 12 predicts less depression ($P=0.045$). Treatment week 8 predicts more depression ($P=0.013$); however, treatment week 16 and 20 predict less depression ($P<0.001$ and $P=0.001$, respectively). By contrast, in male CHB patients, treatment week 8 predicts less depression ($P=0.002$), treatment week 16 and 20 predict more depression ($P<0.001$ and $P=0.024$, respectively). In CHB patients older than 55 years, treatment week 4, 6, 10, 12, 20 and 24 predict less depression ($P=0.002$ for week 20 and $P<0.001$ for all others).

Discussion
Under active assessment of the occurrence and severity of depression during PEG-IFN-based therapy, depression was detected in a biphasic pattern in Taiwanese CHB and CHC patients. To the best of our knowledge, this has not been reported in the literature. Treatment week 8 in CHB patients and treatment week 4 in CHC patients older than 60 years predict more depression. By contrast, treatment week 24 predicts less depression in male patients (Table 2), treatment week 16 predicts less depression in male CHC patients (Additional file 1) and treatment week 16 and 20 predict less depression in CHB patients (Additional file 1). Taking these findings together, treatment week <10 predicts more depression and treatment week >12 predicts less depression, suggesting the predictability of time variables during treatment on occurrence of depression. There was no significant difference in patient characteristics between those who suffered from depression in early phase and in late phase. The biphasic pattern emphasizes the importance of early and active assessment of depression during PEG-IFN-based therapy for its better management.

Virus type predicts depression during PEG-IFN-based therapy. More depression in CHC versus CHB patients under PEG-IFN-based therapy is in-line with a previous comparison study using pooled data from clinical trials of PEG-IFN-α2a therapy for CHB versus CHC patients with a different ethnic background [16]. There has been a debate on which has more effect on depression in chronic hepatitis: the virus, the drug or the ethnic background [18]. Whereas only one of five studies included in the above study with pooled data has combination of ribavirin use, our study included real-world data from consecutive PEG-IFN-α2a or 2b plus ribavirin-treated patients with the same ethnicity. Consistent findings in different drug regimens and in patients with the same ethnicity favour more effect of virus over drug or ethnicity on depression. Although HCV may directly affect the brain [26,27], there have been conflicting results on the role of HCV in occurrence of neuropsychiatric symptoms. Nevertheless, lifetime depression had been reported to be more prevalent in patients with CHC than CHB, irrespective of IFN-α therapy [28]. A database study also confirmed a higher prevalence of depression in CHC than CHB patients [29].

Besides virus type, pre-existing depression is the second independent predictor of more depression in both CHC and CHB patients (Table 2), as well as in CHC.

<table>
<thead>
<tr>
<th>Table 2. GEE for predictors of depression*, including variables with repeated measurements and time variables in all patients</th>
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<tbody>
<tr>
<td><strong>Variables</strong></td>
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<tr>
<td>----------------</td>
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<tr>
<td>CHC versus CHB</td>
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<tr>
<td>Baseline depression</td>
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<tr>
<td>Interaction of male with treatment week 24</td>
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</table>

The variables include: group (chronic hepatitis C [CHC] versus chronic hepatitis B [CHB]), age, male gender, baseline depression, treatment duration (more than versus less than 48 weeks), alanine aminotransferase, baseline haemoglobin, physician A, sustained virological response, and repeated measurements of ribavirin use, sertraline use, erythropoietin use and haemoglobin, as well as time variables: treatment weeks 2, 4, 6, 8, 10, 12, 16, 20 and 24; interaction variables of group with treatment week 2, 4, 6, 8, 10, 12, 16, 20 and 24; and interaction variables of male gender with treatment week 2, 4, 6, 8, 10, 12, 16, 20 and 24. The variables were listed after exclusion one at a time of any variable with a P-value of more than 0.05 ($P=0.151$). Hamilton Depression Rating Scale (HAM-D) score, GEE, generalized estimating equations.

Antiviral Therapy 18.4 571
patients where depression is more prevalent (Additional file 1, Figures 1 and 2). This finding confirms the importance of baseline assessment of depression in patients treated with PEG-IFN-based therapy [6,12,13,15]. The HAM-D scores in our patients were relatively low both at baseline and during treatment in CHB and CHC patients (Figure 2). This is consistent with lower reported incidence of depression in Asian CHB and CHC patients when compared with Caucasian patients under PEG-IFN-based therapy [16], which suggests the effect of cultural influences [30]. Nevertheless, our study in ethnicity with low incidence of depression disclosed the clinical course of depression and its predictors, which highlights the importance of depression assessment to optimize PEG-IFN-based therapy in both CHB and CHC patients.

In CHC patients, higher serum haemoglobin levels were noted in those with more depression (Additional file 1). This may be related to more depression in early treatment period (treatment weeks 6–10), when the serum haemoglobin level was higher than late treatment period (treatment weeks 16–28) when the haemoglobin level was lower (Figure 1).

In CHB patients, longer duration of PEG-IFN therapy predicts more depression during treatment. This finding is in-line with a previous report showing that longer duration of IFN-α treatment may worsen the neuropsychiatric side effects [31]. Baseline high serum HBV DNA level and its level at treatment week 24 predict less depression. Patients with high HBV DNA are in the non-cirrhotic non-advanced stage of disease. A study on health-related quality of life showed better mental dimensions in this disease stage [32]. HBeAg positivity predicts more depression, by contrast HBeAg positivity at treatment week 12 predicts less depression. As depression is less prevalent in HBeAg-positive disease as compared with more advanced disease stage, the association of HBeAg and depression is unclear and has not been reported in the literature. Further study is needed to clarify the interaction between HBeAg and depression in CHB patients. CHB patients older than 55 years correlate with less depression at treatment weeks 4, 6, 10, 12, 20 and 24; this may be because all our CHB patients older than 55 years are male patients who have less depression compared with females.

There were more male gender and younger age in our CHB than CHC patients with active hepatitis receiving PEG-IFN-based treatment, which is in-line with previous reports [33]. The haemoglobin level was higher in the CHB versus CHC patients, which may be related to more CHB patients that are male and of younger age.

Furthermore, socioeconomic factors (marital and employment status) and on-treatment adverse events, such as pyrexia, fatigue, weight loss more than 1 kg, myalgia, headache, nausea, insomnia, hair loss and skin rash may also be important for the development of depression. We added these as well as other variables in the generalized estimating equation for predictors of depression in all (both groups) patients (Additional file 1). Besides the previously mentioned variables, we found pyrexia, insomnia and hair loss were also predictors of depression after adjustment for other variables (Additional file 1).

There are some limitations to this study. First, although each of our patients had multiple repeated HAM-D scores, the enrolled number of patients was relatively small, which lead to uneven distribution of patients in some sub-groups. Second, the low prevalence of depression in our study population further enhances the necessity of larger case numbers. Third, our study did not evaluate other aspects of quality of life that may also be different between CHB and CHC patients receiving PEG-IFN-based therapy.

In conclusion, depression occurred in a biphasic pattern during PEG-IFN-based therapy and should be early and actively assessed, especially in patients with CHC or pre-existing depression.

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Disclosure statement

The authors declare no competing interests.

Additional file

Additional file 1: Detail predictors of depression and smoothing plots for age can be found at http://www.intmedpress.com/uploads/documents/2709_Huang_Add_file1.pdf

References


