Cytokines, Treatment Responses, and Body Weight Changes in Major Depressive Patients Treated with Antidepressants

Chin-Chuen Lin, M.D.¹, Chien-Te Lee, M.D.², Tiao-Lai Huang, M.D.³*

Objectives: Serum cytokine levels are implicated in the action of mechanism for acute-phase major depression. In this study, we intended to investigate the relationships between cytokine serum levels and treatment responses as well as body weight changes after a four-week antidepressant treatment in patients with major depressive disorders. Methods: Fifty-four major depressive patients were recruited. Their serum cytokine levels of interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), interleukin-10 (IL-10), and transforming growth factor β1 (TGF-β1) were examined using ELISA kits. Psychiatric diagnoses were made using the DSM-IV criteria. Severity of major depression was assessed using the 17-item Hamilton Depression Rating Scale. Results: We found significantly lower baseline serum IL-10 level (p = 0.001) and significantly lower baseline IL-10/TGF-β1 ratio (p < 0.01) in responders compared to those in non-responders. In all patients after antidepressant treatment, we found a significant positive correlation between body weight change and TNF-α/TGF-β1 ratio change (p < 0.05). In responders alone, a significant positive correlation between body weight change and TNF-α/TGF-β1 ratio change (p < 0.05) was found. In non-responders, a significant negative correlation between body weight change and IL-10/TGF-β1 ratio change (p < 0.01) was found. Conclusion: Serum levels of TNF-α, IL-10 and TGF-β1 could be used to predict the treatment response and body weight change in patients with major depression.

Key words: antidepressant, body weight, cytokine, major depression


Introduction

Depression has been demonstrated to be accompanied by activation of the immune/inflammatory system, including changes in serum acute phase protein [1, 2] and cytokine levels [3-5]. Cytokine imbalance may play a rôle in the pathogenesis for major depression [6, 7]. In addition, multiple pathways (such as upregulation of sero-
tonin and dopamine transporters) and the activation of indoleamine dioxygenase (which leads to decreased serotonin and increased excitotoxicity) have also been reported to link to inflammation in major depression [8, 9].

Cytokines which are mainly mediated by type 1 T helper (Th1) cells, are often categorized into both pro- and anti-inflammatory cytokines. The former group consists of interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ). The latter group includes interleukin-4 (IL-4) and interleukin-10 (IL-10). They are mainly mediated by Th2 cell [10-12]. TGF-β1 can act as a Th3 cytokine, to inhibit both Th1 and Th2 development and to regulate the balance between Th1 and Th2 cytokines [12-14]. Myint et al. suggested that Th1 and Th2 cytokine imbalance has been observed in subpopulation of depressed patients, and that TGF-β1 can play a role in causing depression [15].

Antidepressant treatment can cause a decreased serum levels of proinflammatory cytokines IL-12 and an increased serum levels of anti-inflammatory cytokines IL-4 and TGF-β1 [16]. Past studies also reported that antidepressants can decrease the Th1/Th2 ratio [17-19]. Fewer studies exist to assess the usefulness of cytokine serum levels to predict treatment response in major depression. Raised pretreatment plasma levels of IL-6 and TNF-α are suggestive of poor response to antidepressant treatment [18, 20]. Molecular and clinical evidences exist in the shared biology of depression and obesity from the stress response regulated by hypothalamic-pituitary-adrenal (HPA) axis [21]. Proinflammatory cytokines, such as IL-1, TNF-α, and IFN-α, and their signaling pathways can acutely stimulate corticotropin-releasing hormone, activate the HPA axis, and impair glucocorticoid receptor (GR) function, causing hyperglycemia, insulin resistance, and body weight change [22, 23].

To understand the relationships between other cytokines and body weight changes in patients with major depression, is worthwhile. In this study, we intended to investigate the relationships between Th1/Th2 cytokine imbalance, treatment response, and body weight changes in major depression in Taiwanese patients.

Methods

Study subjects

This study was done on inpatient wards at Kaohsiung Chang Gung Memorial Hospital from December 2003 to July 2005. This study was approved by institutional review board with the need to have signed informed consent of study subjects. Patients aged 20-65 years diagnosed of major depression were evaluated by the same psychiatrist using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID). The severity of depression was determined using the 17-item Hamilton Depression Rating Scale (HDRS) [24]. Excluded from the study were patients being co-morbid with other psychiatric disorders, those with a HDRS score of less than 20 at baseline, and those with acute infections or having history of allergic reactions.

Study procedures

The patients received only one of the following antidepressants: fluoxetine, venlafaxine, or mirtazapine. Patients were allowed using concomitant sedatives (i.e., lorazepam 3 mg/day or alprazolam 1.5 mg/day) or hypnotic (i.e., zolpidem 10-20 mg/day), but they were not permitted to use any mood stabilizer.

All study patients received examinations for blood pressure, chest X-ray, electrocardiogram,
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and routine blood tests, to be ruled out for any chronic medical illnesses including heart, lung, liver, kidney and metabolic diseases. The patients did not take any psychotropic medications for at least two weeks before they entered into this study (in acute phase).

Laboratory data

Serum of the patients were collected around 8:00 a.m., after they had been fasted for at least 9 hours. Levels of IFN-γ (Th1), TNF-α (Th1), IL-10 (Th2), and TGF-β1 (Th3) were measured using ELISA kits (Amersham Biosciences, Buckinghamshire, UK). We determined all cytokine serum levels according to the manufacturers’ protocols. All assays were carried out by the same technician at our hospital laboratory. The intra-assay and inter-assay variations were all less than 10%, respectively.

Statistical analyses

Participants were divided into responders and non-responders. Responders were defined by having at least 50% reduction of the baseline 17-item HDRS score after a four-week antidepressant treatment [25]. Data were expressed as mean ± standard deviation and were compared by Student t-test. Data analysis was performed with analysis of co-variance (ANCOVA) adjusted for age and gender for group mean differences between groups. Within-subject changes before and after four weeks of antidepressant treatment (endpoint) for each treatment group were evaluated using the paired t-test. Pearson correlations were used to detect relationships between body weight changes, serum cytokine level changes, and ratio changes after a four-week antidepressant treatment.

We completed all data analyses with Statistical Package for Social Science software version 19 for Windows (SPSS, Inc., Chicago, Illinois, USA). The differences between groups were considered significant if p-values were smaller than 0.05.

Results

Fifty-four major depressive patients (14 males and 40 females) were recruited. They were treated with fluoxetine (n = 24, dose range: 20-40 mg/day), venlafaxine (n = 21, dose range: 75-225 mg/day), and mirtazapine (n = 9, dose range: 30-60 mg/day). Among them, 41 patients (11 males and 30 females) were categorized into responders, and 13 patients (3 males and 10 females) were categorized into non-responders.

Table 1 lists demographic data and serum cytokine levels at baseline and endpoints after a four-week antidepressant treatment. Table 2 describes serum cytokine ratios (Th1/Th2, Th1/Th3, and Th2/Th3) among responders and non-responders at baseline and endpoint. And Table 3 shows the correlations between body weight changes, serum cytokine level changes, and ratio changes after a four-week antidepressant treatment.

Discussion

One of the most important finding in this study is the significantly lower IL-10 level (14.6 ± 13.7 pg/mL in the responder group vs. 33.6 ± 43.6 pg/mL in the nonresponder group, p = 0.001, Table 1), and IL-10/TGF-β1 (Th2/Th3) ratio (0.34 ± 0.36 pg/mL in the responder group divided by 0.72 ± 1.07 pg/mL in the nonresponder group, p < 0.01, Table 2) at baseline in the major depressive patients that responded with a four-week antidepressant treatment. In the earlier studies, response to antidepressant is associated with Th1 cytokines.
mostly. Lanquillon et al. found that greater pretreatment IL-6 levels are associated with treatment resistance [18]. Kubera et al. showed that the therapeutic effects of antidepressants are related to IFN-γ/IL-10 ratio (Th1/Th2 ratio), especially in IL-10 (Th2) [17]. O’Brien et al. found that increased pretreatment plasma levels of IL-6 and TNF-α have poor response to antidepressants [20]. Eller et al. found that a higher level of TNF-α can predict a non-response to treatment with esci-

Table 1. Demographic data and serum cytokine levels at baseline between responders and non-responders of antidepressant treatment.

<table>
<thead>
<tr>
<th></th>
<th>Responder (n = 41)</th>
<th>Non-responder (n = 13)</th>
<th>Total (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>11/30</td>
<td>3/10</td>
<td>14/40</td>
</tr>
<tr>
<td>Age</td>
<td>37.3 ± 8.4</td>
<td>36.9 ± 9.5</td>
<td>37.2 ± 9.6</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.1 ± 4.2</td>
<td>22.8 ± 4.4</td>
<td>22.3 ± 4.2</td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>3.6 ± 4.2</td>
<td>2.7 ± 2.8</td>
<td>3.4 ± 3.9</td>
</tr>
<tr>
<td>17-item HDRS</td>
<td>35.1 ± 4.4</td>
<td>34.8 ± 3.9</td>
<td>35.0 ± 4.0</td>
</tr>
<tr>
<td>TNF-α (pg/mL)</td>
<td>0.9 ± 2.2</td>
<td>0.6 ± 2.1</td>
<td>0.8 ± 2.2</td>
</tr>
<tr>
<td>IFN-γ (pg/mL)</td>
<td>10.2 ± 28.1</td>
<td>1.0 ± 2.5</td>
<td>8.0 ± 24.8</td>
</tr>
<tr>
<td>IL-10 (pg/mL)**</td>
<td>14.6 ± 13.7</td>
<td>33.6 ± 43.6</td>
<td>19.2 ± 25.3</td>
</tr>
<tr>
<td>TGF-β1 (ng/mL)</td>
<td>47.5 ± 14.7</td>
<td>44.8 ± 12.5</td>
<td>46.8 ± 14.1</td>
</tr>
</tbody>
</table>

*** Significantly lower (F = 4.222, p = 0.001) for the responder vs. non-responder group in the serum level of IL-10 at baseline in ANCOVA after being adjusted for the factors of age and gender.

17-item HDRS, 17-item Hamilton Depression Rating Scale; ANCOVA, analysis of co-variance; BMI, body mass index.

Table 2. Serum cytokine ratios (Th1/Th2, Th1/Th3 and Th2/Th3) between responders and non-responders of antidepressant treatments at baseline and endpoint.

<table>
<thead>
<tr>
<th></th>
<th>Responder (n = 41)</th>
<th>Non-responder (n = 13)</th>
<th>Total (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TFN-α/IL-10 at baseline (pg/mL)</td>
<td>0.11 ± 0.32</td>
<td>0.04 ± 0.14</td>
<td>0.10 ± 0.29</td>
</tr>
<tr>
<td>TNF-α/IL-10 at endpoint (pg/mL)</td>
<td>0.33 ± 1.53</td>
<td>0.00 ± 0.00</td>
<td>0.25 ± 1.34</td>
</tr>
<tr>
<td>IFN-γ/IL-10 at baseline (pg/mL)</td>
<td>0.40 ± 1.52</td>
<td>0.00 ± 0.00</td>
<td>0.31 ± 1.33</td>
</tr>
<tr>
<td>IFN-γ/IL-10 at endpoint (pg/mL)</td>
<td>1.04 ± 3.01</td>
<td>0.40 ± 1.46</td>
<td>0.88 ± 2.73</td>
</tr>
<tr>
<td>TNF-α/TGF-β1 at baseline (pg/mL)</td>
<td>0.02 ± 0.04</td>
<td>0.01 ± 0.04</td>
<td>0.01 ± 0.04</td>
</tr>
<tr>
<td>TNF-α/TGF-β1 at endpoint (pg/mL)</td>
<td>0.05 ± 0.21</td>
<td>0.00 ± 0.00</td>
<td>0.04 ± 0.18</td>
</tr>
<tr>
<td>IFN-γ/TGF-β1 at baseline (pg/mL)</td>
<td>0.18 ± 0.46</td>
<td>0.04 ± 0.09</td>
<td>0.15 ± 0.40</td>
</tr>
<tr>
<td>IFN-γ/TGF-β1 at endpoint (pg/mL)</td>
<td>0.27 ± 0.54</td>
<td>0.25 ± 0.61</td>
<td>0.26 ± 0.55</td>
</tr>
<tr>
<td>IL-10/TGF-β1 at baseline (pg/mL)**</td>
<td>0.34 ± 0.36</td>
<td>0.78 ± 1.07</td>
<td>0.44 ± 0.63</td>
</tr>
<tr>
<td>IL-10/TGF-β1 at endpoint (pg/mL)</td>
<td>0.35 ± 0.39</td>
<td>0.47 ± 0.71</td>
<td>0.38 ± 0.48</td>
</tr>
</tbody>
</table>

** Significantly lower (F = 3.368, p < 0.01) in the responder vs. the non-responder group in the serum level ratio of IL-10/ TGF-β1 at baseline in ANCOVA after being adjusted for the factors of age and gender.

Th1, type 1 T helper cells; Th2, type 2 T helper cells; Th3, type 3 T helper cells; TNF-α, tumor necrosis factor-α; IL-10, interleukin-10; IFN-γ, interferon-γ; TGF-β1, transforming growth factor β1; ANCOVA, analysis of co-variance.
talopram, and that the changes in soluble IL-2 receptor levels during the treatment are different in responders and non-responders [26]. In a more recent study, an association between the rs114643 variant of the IL-1B gene and non-remission after antidepressant treatment and decreased amygdala and anterior cingulate cortex function has been found [27]. The results of this study did not show that Th1 cytokines or Th1/Th2 ratios could be used to distinguish the differences between responders and non-responders (Tables 1 and 2). Our data imply that Th2 or Th3 cytokines have a more prominent rôle than Th1 cytokines in predicting the treatment response of major depression. While the results of our study are not entirely consistent with those of past studies, the interaction between antidepressants, cytokines, and major depression might just be more complicated than we have anticipated.

Our another study finding (Table 3) was the significant positive correlation between body weight change and TNF-α/TGF-β1 (Th1/Th3) ratio change ($p < 0.05$) after a four-week antidepressant treatment in responder and non-responder groups of major depressive patients. That correlation remained significant when only the responders were analyzed ($p < 0.05$). Examining the data of non-responders, we found that significant negative correlation with body weight change existed ($p < 0.01$) only in the IL-10/TGF-β1 (Th2/Th3) ratio change. Those results of the study suggest that the body weight change in responder and non-responder patients might have different immune pattern. In previous studies, the relationships of body weight or body mass index (BMI) and antidepressant response have been discussed [28]. Serum cytokines TNF-α and IL-6 have been used as biological correlates in the studies of obesity.

### Table 3. The correlations between body weight changes and serum cytokine levels and ratio changes after patients taking antidepressants over a period of four weeks

<table>
<thead>
<tr>
<th></th>
<th>Responder (n = 41)</th>
<th>Non-responder (n = 13)</th>
<th>Total (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta$TNF-α (pg/mL)</td>
<td>0.15</td>
<td>-0.40</td>
<td>0.08</td>
</tr>
<tr>
<td>$\Delta$IFN-γ (pg/mL)</td>
<td>-0.19</td>
<td>-0.30</td>
<td>-0.20</td>
</tr>
<tr>
<td>$\Delta$IL-10 (pg/mL)</td>
<td>0.19</td>
<td>-0.36</td>
<td>-0.16</td>
</tr>
<tr>
<td>$\Delta$TGF-β1 (ng/mL)</td>
<td>-0.02</td>
<td>0.16</td>
<td>0.06</td>
</tr>
<tr>
<td>TNF-α/IL-10 change</td>
<td>0.22</td>
<td>0.40</td>
<td>0.19</td>
</tr>
<tr>
<td>IFN-γ/IL-10 change</td>
<td>0.20</td>
<td>0.28</td>
<td>0.15</td>
</tr>
<tr>
<td>TNF-α/TGF-β1 change</td>
<td>0.35*</td>
<td>0.40</td>
<td>0.29*</td>
</tr>
<tr>
<td>IFN-γ/TGF-β1 change</td>
<td>-0.13</td>
<td>0.11</td>
<td>-0.09</td>
</tr>
<tr>
<td>IL-10/TGF-β1 change</td>
<td>0.03</td>
<td>-0.71**</td>
<td>-0.21</td>
</tr>
</tbody>
</table>

* Significantly having positive correlation between body weight change and the ratio of TNF-α/TGF-β1 change in both responder group ($p < 0.05$), and total patients ($p < 0.05$)

** Significantly having negative correlation between body weight change and the ratio of IL-10/TGF-β1 change in non-responder group ($p < 0.01$)

TNF-α, tumor necrosis factor-α; IL-10, interleukin-10; IFN-γ, interferon-γ; TGF-β1, transforming growth factor β1; ANCOVA, analysis of co-variance $r$ value, with the body weight change (kg/week) as the dependent variable, and changes of cytokine levels and cytokine ratios as independent variables.
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[21, 29-33]. In addition, Schiepers et al. have demonstrated the relationships between the central action of cytokines and HPA axis, suggesting the possible mechanisms of cytokine-induced depression [7]. Proinflammatory cytokines, such as IL-1, IL-2, IL-4, TNF-α, and IFN-α, and their signaling pathways can impair glucocorticoid receptor (GR) function [22, 23]. These listed cytokines could induce glucocorticoid resistance through the mechanisms, such as preventing the entry of the cortisol-GR complex into the nucleus and preventing the binding of the complex to the DNA [34]. In a recent study, increased GR density has been found to be correlated with BMI, percentage body fat, waist circumference, and insulin resistance, but no differences have been observed between Caucasian and African American subjects or male and female participants [35]. But the rôles of IL-10 (Th2) and TGF-β1 (Th3) in the body weight of treatment response have been less explored by the investigators on this topic. In earlier studies, TGF-β1 has been proposed to be able to regulate the imbalance between Th1 and Th2 cytokines and to play an important rôle in maintaining tolerance including the central nervous system [15, 36]. The pathophysiological interaction between body weight change, cytokines, and treatment response in major depression requires further investigations.

Limitations of this study

The readers are cautioned not to over-interpret the results of this study because it has four limitations:

- A recent meta-analysis has shown that increased serum levels of TNF-α and IL-6 are the most replicated in major depression, so the inclusion of a wider range of cytokines should be considered [37].

- Smoking can increase the serum levels of inflammatory markers, so relevant data about patients’ smoking status should be included for analysis in the future.

- Different antidepressants might have different immunomodulatory actions of mechanisms. Norepinephrine may mediate a Th2 shift, and serotonin a Th1 shift [38]. If this study would have a larger sample size, immunomodulation differences between types of antidepressants should be analyzed.

- This study has the treatment duration of only four weeks, and future studies need to have a longer observation time to see whether body weight changes after antidepressant treatment and whether different antidepressants have different effects on weight changes.

Conclusion

In this study, we found that responder patients had significantly lower serum levels of IL-10 and IL-10/TGF-β1 at baseline compared to non-responder patients. Based on those study findings, we suggest that serum IL-10 and TGF-β1 could be used to predict the treatment response in patients with major depression in Taiwan. In this study, we also found significant positive correlation between body weight change and TNF-α/TGF-β1 ratio change after a four-week antidepressant treatment in responder and non-responder groups of major depressive patients. That correlation remained significant when only the responders were analyzed. Examining the data of non-responders, we found that significant negative correlation with body weight change existed only in the IL-10/TGF-β1 ratio change. The correlation between TNF-α, IL-10, and TGF-β1 ratio changes and body weight change, warrants further investigations.
Acknowledgements

This work was supported by a clinical research grant from the National Science Council (NSC93-2314-B-182A-204) in Taiwan. We also thank for the help of Genomic and Proteomic Core Laboratory, Department of Medical Research, Kaohsiung Chang Gung Memorial Hospital. The authors declare that they do not have potential conflict of interest in writing this report.

References


