

Blood Biological Markers for Prediction of Escitalopram Response in Patients with Major Depressive Disorder: Preliminary Study

Masato Yamana, Kiyokazu Atake, Asuka Katsuki, Hikaru Hori and Reiji Yoshimura*

Department of Psychiatry, University of Occupational and Environmental Health, Japan

Abstract

Introduction: Lots of studies have been performed to predict the response to antidepressants in patients with major depressive disorder. The findings were however controversial.

Objective: The aim of the present study was to investigate the relationship between response to escitalopram and several peripheral biomarkers in major depressive disorder (MDD).

Material and Methods: Forty-eight MDD patients diagnosed by DSM-IV-TR were enrolled the study, and all were treated with escitalopram. The end-point of the study was 8 weeks after starting the treatment. Twenty-seven patients were completed the study. Their depressive symptoms were evaluated using the 17-items Hamilton Rating Scale for Depression (HAM-D17). The patients whose HAM-D17 reduced 50% or more at 8 weeks were defined as responders. The peripheral biomarkers were assayed with ELISA or high-performance liquid chromatography.

Results: Plasma 3-methoxy-4-hydroxyphenyl glycol (MHPG) level at starting escitalopram in the responders were significantly higher than those in nonresponders ($p = 0.0032$). Any other factors were not different between the responders and the nonresponders.

Conclusion: These results suggest that MHPG level can predict the response to escitalopram.

Keywords: Escitalopram; Catecholamines; Neurotrophic factors; Cytokines; Major depressive disorder; Prediction

Introduction

Catecholamines, neurotrophic factors and cytokine play important role for pathophysiology of major depressive disorder (MDD). We previously reviewed plasma levels of catecholamines predict the response to treatment with antidepressants [1]. Briefly, paroxetine, a selective serotonin reuptake inhibitor (SSRI) had better response to the patients with higher plasma levels of 3-methoxy-4-hydroxyphenylglycol (MHPG), a major metabolite of norepinephrine, whereas, milnacipran, a serotonin, norepinephrine reuptake inhibitor (SNRI), had better response to those who with lower MHPG levels [2]. However, no changes in plasma MHPG switching paroxetine to milnacipran between the responders to nonresponders with milnacipran treatment in MDD patients [3]. Serum levels of brain-derived neurotrophic factor (BDNF) decrease in MDD patients compared with healthy control [4]. A negative correlation was found between serum BDNF levels and Hamilton Rating Scale for Depression (HAM-D) [1]. Antidepressants increase plasma BDNF levels in MDD patients [4]. We also reported that treatment with paroxetine, a SSRI and milnacipran, a SNRI, increased plasma levels of brain-derived neurotrophic factor (BDNF) in responders to those antidepressants [5]. From these findings into account, serum BDNF is one of candidate for biological markers of severity of depressive state. On the other hand, interleukin 6 (IL-6) and tumor necrotic factor- α (TNF- α) in MDD patients were higher than those in healthy control [6]. We reported that serum IL-6 levels were lower in MDD patients compared with sex, and age-matched healthy controls [7]. It is however controversial that serum levels of BDNF or IL-6 predict response to treatment with antidepressants. A report demonstrated patients with higher serum BDNF had better response [8], other did not [7]. We reported that responders to SSRI were significantly higher serum IL-6 levels than nonresponders suggesting serum IL-6 might be a predictor for SSRI response in MDD patients [9]. Kotan et al. [10] reported that serum vascular endothelial growth factor (VEGF) was related with MDD.

In the present study, we investigated between the response to escitalopram, a SSRI and serum levels of BDNF, cytokines (interleukin 2 (IL-2), IL-6, TNF- α), vascular endothelial growth factor (VEGF), and plasma levels of MHPG and homovanillic acid (HVA), a major metabolite of dopamine, in MDD patients.

Subjects and Methods

Forty-eight patients diagnosed MDD using DSM-IV-TR were enrolled in the present study. The demographics data were shown in Table 1. All participants were treated with only escitalopram. The severity of the patients' depressive symptoms was evaluated using the 17-items of Hamilton Rating Scale for Depression (HAM-D17) at each week. The end point of the follow up period was 8 weeks. The patients who decreased their HAM-D17 scores 50 % or more were defined as responders. Others were defined as nonresponders. The blood was drawn once just before starting escitalopram treatment. Their serum levels of BDNF, IL-2, IL-6, TNF- α , and VEGF were assayed by ELISA using Milliplex MAP Kit (HCYTOMAG-60K and HNDG3MAG-36K) on a Milliplex Analyzer 4.2 MAGPIX machine (Millipore) according to the manufacturer's instructions. Analyses included IL-2, IL-6, TNF- α , VEGF, and BDNF. Their plasma levels of

***Corresponding author:** Reiji Yoshimura, Department of Psychiatry, University of Occupational and Environmental Health, 1-1 Iseigaoka, Yahatanishi-ku, Kitakyushu, Fukuoka 8078555, Japan, Tel: +81936917253; Fax: +81936924894; E-mail: yoshi621@med.uoeh-u.ac.jp

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	Responder (n = 20)	Non-responder (n = 28)	P-value
Age	53.7 ± 15.1	58.6 ± 17.3	0.481*
Gender(male/Female)	10/10	2/5	0.591**
Esc max dose (mg/day)	18.0 ± 4.14	16.0 ± 5.47	0.860*
Depressive episodes before ESC treatment	1.87 ± 1.64	1.20 ± 0.44	0.148*
Baseline HAM-D17	20.5 ± 7.21	19.6 ± 3.05	0.430*

Table 1: P-value calculated using student's T-test* and chi-square test**

metabolites of catecholamine were measured using high-performance liquid chromatography with electrochemical detection. The study protocol was approved by the Ethics Committee of the University of Occupational and Environmental Health. Written informed consent was obtained from all participants. Twenty-seven patients of 48 MDD patients (56.25%) completed the present study. The reasons for drop out the present study were the protocol violation (15 patients), moved to other hospitals (4 patients), or the study withdrawal (22 patients).

Results

Response to escitalopram treatment

No significant differences were observed in demographic background between the responders and the nonresponders to escitalopram (Table 1). The response rate at 8 weeks with escitalopram treatment was 41.7%. The dose of escitalopram at week was 16.2 ± 6.2 (mean ± standard deviation).

Plasma levels of catecholamine metabolites and response to escitalopram treatment

Plasma MHPG levels at starting escitalopram in the responders were significantly higher than those in nonresponders ($p = 0.0032$). No difference was found in plasma HVA levels between the responders and nonresponders ($p = 0.5981$) (Figure 1). We further calculated cut-off value by using Receiver Operating Characteristic Curve (ROC), and found the cut-off value was 8.0 ng/ml (sensitivity; 90.0%; specificity; 85.7%) (Figure 2).

Serum levels of BDNF and VEGF and response to escitalopram

No differences were observed regarding serum levels of BDNF and VEGF at starting escitalopram between the responders and nonresponders ($p = 0.2763$, $p = 0.3029$) (Figure 3).

Serum levels of cytokines and response to escitalopram

No differences were observed regarding serum levels of IL 2, IL 6, and TNF-alpha at starting escitalopram between the responders and nonresponders ($p = 0.4577$, $p = 0.4873$, $p = 0.8330$) (Figure 4).

Gender difference for biological markers

There were not any gender differences for prediction of escitalopram response in MHPG, HVA, BDNF, VEGF, IL2, IL 6, and TNF-alpha ($p = 0.6908$, 0.4299 , $p = 0.9588$, $p = 0.4846$, $p = 0.2893$, 0.3569 , 0.6054).

Discussion

The main finding of the present study was plasma MHPG level at starting escitalopram predicted its response in patients with MDD. Patients whose plasma MHPG 8ng/ml or more was prone to better response. Whereas, plasma HVA level, serum levels of BDNF, VEGF, IL 2, IL 6 were not related to the response to escitalopram. The results of the present study were partially in accordance with our previous studies regarding plasma MHPG level. On the other hand, serum IL

6 level was not different between the responders and nonresponders. We recently reported that higher serum IL 6 was associated with response to SSRI. The discrepancy between the present result and our previous one remains unknown. The patients who enrolled in our previous study was treated with only sertraline or paroxetine, but not escitalopram. The difference in the SSRI may one of the reasons. We investigated baseline serum BDNF levels and the response to several antidepressants in MDD patients, also found that no association was observed between serum BDNF and response to antidepressants treatment [1,11]. The result in the present study was reconfirmed in patients with escitalopram treatment. Ventriglia et al. [12] reported that baseline serum VEGF levels did not predict the response to SSRIs. In addition, the authors also demonstrated that treatment with SSRIs did not alter VEGF levels in MDD patients. The result regarding VEGF in the present study was not contradict Ventriglia's finding

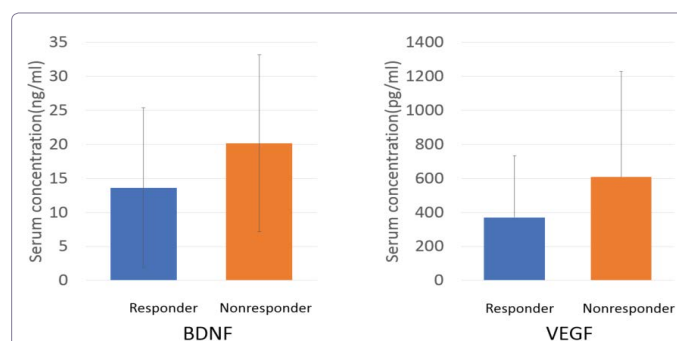


Figure 1: Serum levels of BDNF and VEGF in the responders or nonresponders to escitalopram. Vertical bar means standard deviation.

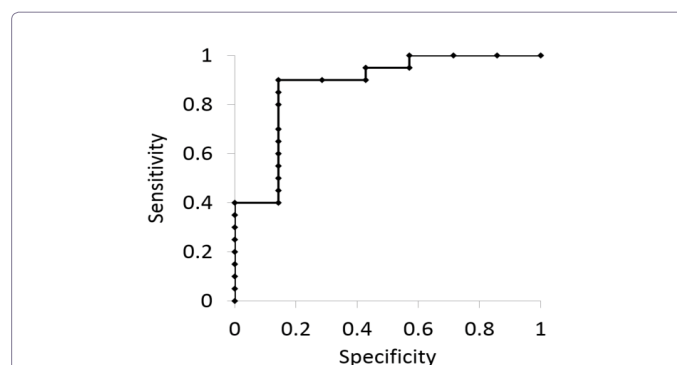


Figure 2: Receiver Operating Characteristic Curve in MHPG.

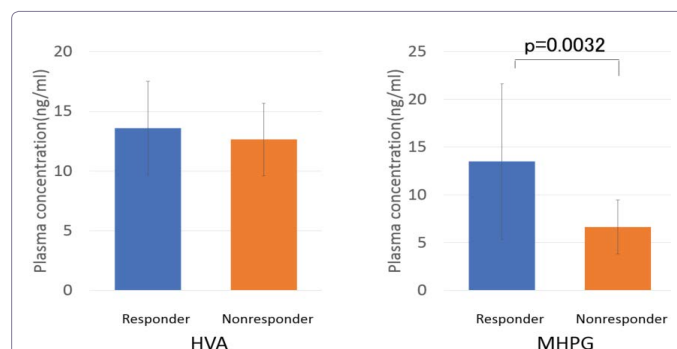
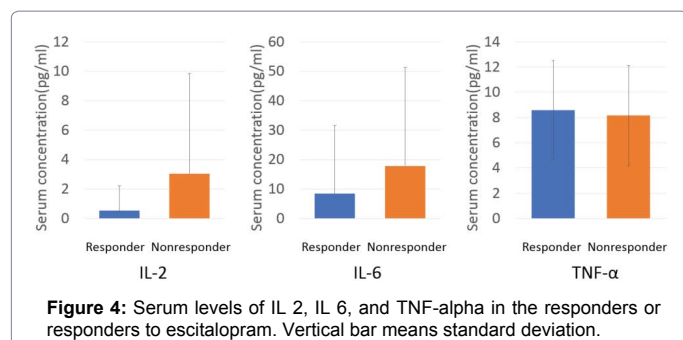


Figure 3: Plasma levels of HVA and MHPG in the responders or nonresponders to escitalopram. Vertical bar means standard deviation.



[12]. The weakest point in the present study was lacked in data at after escitalopram treatment. In other words, we predicted the response to escitalopram treatment at only one point. It remains unknown from the present data that treatment with escitalopram changes the biological markers or not, which is associated with the improvement of depressive symptoms or not. To elucidate this question, we should accumulate larger samples and follow up biological markers. We are now starting longitudinal study for biological markers. Furthermore, we should also combine genetic, proteolytic, and neuroimaging data with our preliminary findings. This process will lead to find a robust biological marker to predict response to escitalopram in MDD. In conclusion, plasma MHPG level at baseline could predict the response to escitalopram in MDD patients. Its cut-off value was 8 ng/ml.

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