

A Practical Utility and Benefit of Pharmacogenetic-based Antidepressant Treatment Strategy for Major Depressive Disorder Patients with Difficult-to-treat

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Objective: We report the results of pharmacogenomics-based antidepressant treatment (PGXt) results in treating treatment-resistant major depressive disorder (TRD) patients in real practice.

Methods: Nine patients were prescribed Neuropharmagen[®] for selection of antidepressants for individual patient and their clinical outcomes were followed.

Results: After treatment by PGXt results from current antidepressants, substantial reduction of depressive symptoms was observed at some point and maintained during observation period in six patients.

Conclusion: Our case series potentially shows the clinical utility and benefit of PGXt for treatment of TRD patients.

KEY WORDS: Treatment; Depressive disorder; Antidepressive agent; Treatment-resistance; Clinical outcome.

INTRODUCTION

The selection of antidepressant for patients with major depressive disorder (MDD) usually depends on clinical intuition, experience and preference of treating physician and thus burden from “trial-and-error” is one of barriers in fast and proper antidepressant treatment for MDD patients in routine practice. Pharmacogenomics-based antidepressant treatment (PGXt) has been recently proposed and promoted as one of available treatment options toward precision medicine in MDD [1].

According to a recent independent survey with 156 clinicians, more than 80% of participants agreed that pharmacogenomic variants may affect drug responses and have clinical utility [2]. Interestingly another survey (psychiatrists, n = 5,316 : neurologists, n = 2,167) [3] indicated the differential experience of genetic testing be-

tween psychiatrists and neurologists despite of several common patient populations; neurologists had 5 times higher experience with genetic tests than psychiatrists in a past 6 months. The most commonly ordered categories of tests were related to stroke, neuromuscular disorders, and movement disorders for neurologists; and pharmacogenomics for psychiatrists [3].

There have been a number of clinical studies investigating PGXt effects using different methodologies [1,4-12]. According to a recent meta-analysis [13] comparing commercial PGXt kits, the pooled risk ratio for treatment response and remission of PGXt versus treatment as usual were 1.36 and 1.74, respectively, which are all in favor of PGXt. A number of PGXt tool kits have been available and studied and commercialized for routine practice, however, none of these has become common use in routine clinical practice [14].

Hence, following case series of PGXt use may enhance and promote the understanding of clinicians for practical utility and benefits of PGXt in treatment of treatment-resistant depression (TRD) patients in routine practice.

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METHODS

All data was taken from medical records.

The PGXt was prescribed by the consent of individual patient since it is not covered by government insurance in Korea, meaning that all patients were fully responsible for its payment. For brief summary of PGXt, the saliva was collected into prepared easy kit and then sent to the central lab located in Barcelona. The result was available after two to three weeks after delivery to the lab. The full results were provided on the designated website (<http://international.neurofarmagen.com>) upon receiving the email notice to the clinician. The final results were graphically presented with four color code as follows: 1) green (increased likelihood of positive response and/or lower risk of adverse drug reactions), 2) red (increased risk of adverse drug reactions), 3) yellow (need for drug dose monitoring and/or less likelihood of positive response), and 4) white (described as standard, no genetic variants relevant to the treatment have been found. use as directed). More detailed genetic information including drug-drug interaction was also provided in the final results [1].

All subjects were treated by selected antidepressants based on the results from PGXt. All the PGXt results were thoroughly provided to individual patient upon receiving the results of PGXt and patients were told about next and future treatment strategy with the use of PGXt results such as application of augmentation, combination, and switching of all current psychotropics including antidepressant. Individual patient actively participated in the treatment decision along with treating clinician.

Available clinical information including Montgomery–Åsberg Depression Rating (MADRS) was collected.

The remission was defined as having ≤ 10 in MADRS total score at any visit point. Observation period was not specifically defined since the present study tried to find clinical outcomes in a naturalistic setting and follow-up period was quite different among all subjects.

This retrospective study was approved by institutional review board (IRB) of Bucheon St. Mary's Hospital (IRB approval number. HC20RISI0009).

RESULTS

Thirteen patients were tested by the PGXt in routine

practice. Minimum follow-up time was 106 days (case 7) and the longest was 3 years (case 4). Three were diagnosed with schizophrenia and another one was a foreigner who just wanted to test his genotypic profile for comparison of current antidepressant since he has been treated with same antidepressants more than 10 year with moderate response and some adverse events. Therefore, 9 patients were included in this study. Detailed clinical information is presented in Table 1. Six patients remitted as of the last follow-up point. The mean remission time was 80.5 days after treatment of PGXt ($n = 6$), while the response time was 37.3 days ($n = 6$).

Case 1

Mr. A is a 22-year-old male college student who has been continuously depressed and treated by foreign psychiatrist while studying abroad. His first-degree relatives had suffered from MDD (attempted suicide history). Main symptoms included depressed mood, loss of interest, lack of energy, concentration difficulties, insomnia, and loss of hope, as well as fear to AEs from antidepressants. He previously tried all SSRIs without proper effects but suffered AEs including sedation, anxiety and decreased cognitive function. Based on his PGX, bupropion 300 mg/d was applied for one week, but he complained a severe headache and thus it was decreased to 150 mg/d for 7 days and increased to 300 mg/d for next 2 weeks after disappearance of headache. His depressive symptoms were remitted at day 51; he reported his function was completely restored and went back to foreign country to continue his study.

Case 2

Mrs. B is a 44-year-old female working as a teacher. Her symptoms included depressed mood, frequent tiredness, lack of energy, decreased concentration, emotional fluctuation, sleep disturbance, and anxiety. She was also sensitive to AEs of previous antidepressants and suffered lack of treatment response. As seen in Table 1, she had failed to show proper response from previous antidepressant treatment. After switching to escitalopram, her long-standing AE, mild hand tremor and dry mouth substantially reduced and remission was observed at 94 days of PGXt maintaining till today.

Case 3

Mrs. C is a 43-year-old female, a health professional.

Table 1. Demographics and clinical/PGXt information of the patients at the time of prescription of Neuropharmagen®

Case	Age/Sex/ DOT (yr)	Baseline treatments (mg/d)	Current AD DOT	Green	Red	Yellow	Standard	Applied AD	Time of remission (days)	Time of response (days)
1	22/M/3	EPAM 20/ LMTG 200	66 days	None	CTAM/EPAM/FOX/ PRX/FVX/SERT	AGO/IMI/NTP/VFX/VTX/AMI/ CMI/DXP/MSR/DSP/DLXT/MIR	DVFX/TZD/BPR	BPR 300	51	51
2	44/F/15	a.PRX 20/ b.PRX 20/ VFX 75 c.TNT 25/ FOX 20/ ARP 5	From 2011.08.12. Last more than 1 years maintain	CTAM/EPAM	None	None	FOX/PRX/FVX/SERT/AGO/IMI/ NTP/DVFX/VTX/AMI/CMI/DXT/ MSR/DSP/DLXT/MIR/VFX/TZD/ BPR	EPAM 10	94	34
3	43/F/3	a.FOX 10 b.SERT 50 c.EPAM 5 d.VTX 5	More than 2 years	None	CTAM/EPAM/FOX/ PRX/FVX/SERT	IMI/NTP/VTX/AMI/CMI/DXP/ MSR/DSP/DLXT/MIR/VFX	AGO/BPR/DVFX/TZD	BPR 150	NA	NA
4	51/F/5	a.PRX 30	86 days	FOX/FVX	None	CTAM/EPAM/IMI/AMI/CMI/ DXP/SERT	AGO/DVFX/NTP/MSR/PRX/VFX/ BPR/DSP/DLXT/MIR/VTX	FOX 20/ MIR 30	91	15
5	45/M/7	a.SERT 150 b.MIR 15	156 days	None	CTAM/EPAM/FOX/ PRX/FVX/SERT	AGO/IMI/NTP/VFX/VTX/AMI/ CMI/DXP/MSR/DSP/DLXT/MIR	DVFX/TZD/BPR	MIR 15/ LIC 300	105	46
6	54/F/4	MIR 15/ DVFX 150	3 years	CTAM/EPAM/ FOX/FVX/ SERT	PRX	None	AGO/DVFX/IMI/NTP/TZD/VTX/ AMI/CMI/DXP/MSR/BPR/DSP/ DLXT/MIR/VFX	EPAM 10/ MPD 10/ MIR 7.5	93	50
7	54/M/1	FOX 20	56 days	None	None	CTAM/EPAM/IMI/AMI/CMI/ DXP/SERT	AGO/DVFX/NTP/MSR/PRX/VFX/ BPR/DSP/DLXT/MIR/VTX	VTX 10	49	28
8	23/F/3	SERT 150 PRX 30	180 days	None	CTAM/EPAM/FOX/ PRX/FVX/SERT	None	AGO/DVFX/IMI/NTP/TZD/VTX/ AMI/CMI/DXP/MSR/BPR/DSP/ DLXT/MIR/VFX	LIC 600 MIR 15	NA	NA
9	38/F/2.8	EPAM 20 SERT 100	84 days	None	CTAM/EPAM/FOX/ PRX/FVX/SERT	IMI/NTP/VTX/AMI/CMI/DXP/ MSR/DSP/DLXT/MIR/VFX	AGO/BPR/DVFX/TZD	EPAM → BPR/VFX	NA	NA

PGXt, pharmacogenomics-based antidepressant treatment; AD, antidepressant; DOT, duration of treatment; Above data represent the AD response only; PRX, paroxetine; EPAM, escitalopram; TNT, tianeptine; ARP, arripiprazole; FOX, fluoxetine; VTX, vortioxetine; MIR, mirtazapine, SERT, sertraline; VFX, venlafaxine; AGO, agomelatine; IMI, imipramine; NTP, nortriptyline; CMI, clomipramine; MSR, mianserine; DLXT, duloxetine; DXP, doxepin; DSP, desipramine; AMI, amitriptyline; BPR, bupropion; DVFX, desvenlafaxine; LIC, lithium; MPD, methylphenidate.

Her symptoms included depressed mood, sadness, sensitiveness, irritability, sweating, lack of energy, agitation, anxiety, and sleep disturbance. She suffered AE from previous antidepressants and thereby usually treated with subtherapeutic dosages without achievement of adequate response. After switching to bupropion, reduction of core depressive symptoms, improvement of tremulousness, improvement of energy and cognition was observed but not reached a remission (MADRS: 20 to 15, 25.0% decrease) till 2 months of PGXt.

Case 4

Mrs. D is a 51-year-old female, a house-wife. Her symptoms included depressed mood, irritability, fluctuation of mood, agitation, severe anxiety, severe sleep disturbance, emptiness, loneliness, and loss of volition. After 2 months treatment with paroxetine, her core depressive symptoms were not properly improved. After switching to fluoxetine and mirtazapine, dramatic improvement of sleep disturbance and reduction of core depressive symptoms were found and remission was achieved at 91 days of PGXt maintaining till today.

Case 5

Mr. E is a 45-year-old male, working at a business company. He suffered from multiple episodes of suicidal attempt and continuous feeling of suicidal ideation, depressed mood, irritability, inferiority, significant reduction of productivity, sleep disturbance, and hopelessness. Despite of different classes of antidepressant treatments, his depressive symptoms were not improved. After switching to mirtazapine, improvement of sleep and depressive symptoms were noted at day 14 and remission was achieved at 105 days of PGXt maintaining till today. Based on his report, his functional recovery has been the highest over 5 years.

Case 6

Mrs. F is a 54-year-old female, a gemologist. Her symptoms included severe depressed mood, sadness, lack of interest, social withdrawal, numbness, lack of energy, agitation, anxiety, and sleep disturbance. She had multiple episode of MDD and visited multiple doctors for seeking better treatment. Her core depressive symptoms retained and never remitted since her treatment with multiple antidepressants after onset of MDD. In addition, she was very

sensitive to AEs from antidepressants. After switching to escitalopram, reduction of core depressive symptoms was observed with 2 weeks, however, sleep was not improved; mirtazapine was added up and thereafter her sleep was also substantially improved. To augment therapeutic response, methylphenidate was also added. Remission was observed at 93 days after PGXt maintaining till today. Based on her and husband, she never has been as good as now since the onset of MDD.

Case 7

Mr. G is a 54-year-old male, a health professional. He suffered continuous feeling of loneliness, lack of motivation, lack of energy, and sadness for 1 years; fluoxetine 20 mg/d was successful for treatment of his depressive symptoms for a while, however, mild hand tremor was critical AE to him and thus PGX was done. Vortioxetine was selected and it successfully reduced his tremor and remission was also noted at day 49.

Case 8

Ms. H is a 23-year-old female, a student. She suffered suicidal ideation, depressed mood, irritability, sleep disturbance, moderate anxiety, decreased productivity, decreased concentration, and lack of volition. Despite of longstanding treatment with sertraline and paroxetine, her depressive symptoms were not significantly improved and also suffered from AEs, headache, hand tremor, worsening of anxiety, and weight gain. After switching to mirtazapine, improvement of sleep and depressive symptoms were noted at day 14, moderate functional recovery was observed at 2 months of PGXt maintaining (MADRS: 21 to 14, 33.3% decrease) aftermath but remission was not achieved. However, her parents reported that she has never been as good as now since the onset of depression.

Case 9

Mrs. I is a 38-year-old female, a house-wife. She suffered from chronic episode of depression including symptoms of depressed mood, guilty feeling, incompetence as a wife and parents, decreased social activity, sleep disturbance, lack of energy/volition, sensitiveness, and tiredness. Despite of different classes of antidepressant treatments approximately for 3 years, her depressive symptoms were not much improved. After switching to bupropion, mild improvement of anxiety and sleep disturbance were noted at day

40 but remission was not achieved till at 123 days (MADRS: 30 to 23, 23.3% decrease). She wanted to find better treatment and thereby she was eventually referred to another hospital with PGXt results as she wanted.

DISCUSSION

Indeed numerous similar studies have shown the effectiveness and tolerability of PGXt for treatment of TRD patients [4-12], however, the current evidence of PGXt is not yet enough for routine use in daily practice. Although widespread clinical applications of PGXt is still far away from routine practice, available results potentially suggest that PGXt may be a practical tool to guide antidepressant treatment. Hence, the US Food and Drug Administration included PGXt indications in the labeling of several antidepressants [15]. Provisional PGXt guidelines have been also developed and continuously revised to track down the rapid progress of modern PGX study results [7,16,17]. The Clinical Pharmacogenetics Implementation Consortium has also continuously published updated-guidelines for relevant information for PGXt [1].

Most current treatment guidelines suggest switching, combination, and augmentation strategies upon a failure of current antidepressant treatment providing inadequate response despite of proper treatment (dose/duration, etc.) in routine practice; however, blind and empirical choice of next antidepressant is also away from systematic and scientific strategy not guaranteeing a successful treatment [18-23]. In addition early treatment response is known to determine the ultimate clinical outcomes, indicating a need of fast and correct treatment decision pathway [24,25]. Therefore, PGXt targeting a precision medicine can prompt, facilitate, and widen proper treatment choice for such TRD patients in busy daily practice [24].

In this context our case series with successful PGXt potentially showed its clinical utility and benefit for patients with TRD in routine practice. Sufficient evidence from adequately-powered and well-designed studies should be necessary for clinicians to ensure the utility of PGXt in routine practice.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Conceptualization: Chi-Un Pae. Protocol development: Chi-Un Pae. Draft writing: Kyung Ho Lee, Chi-Un Pae. Intellectual comments and critics on the content: Alessandro Serretti, Won-Myong Bahk, Soo-Jung Lee. Data acquisition: Chi-Un Pae, Kyung Ho Lee. Data analysis: Chi-Un Pae.

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