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R347C Polymorphisms in ADRA1A Genes and Mirtazapine Treatment Response in Koreans with Major Depression

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Objectives Adrenergic alpha 1 and 2 receptors work as pathways to control the serotonergic neuron moderation and mirtazapine acts as antagonist of these receptors. The adrenoreceptor alpha 1a (ADRA1A) gene, which encodes adrenergic alpha 1 receptor, has Arg-347Cys genetic polymorphism and the polymorphism has strong relationship with many neuro-psychiatric diseases. In this study, we explored the relationship between ADRA1A R347C polymorphism and mirtazapine treatment response in Koreans with major depression.

Methods 352 patients enrolled in this study, and the symptoms were evaluated by 17-item Hamilton Depression Rating (HAMD-17) scale. After 1, 2, 4, 8, and 12 weeks of mirtazapine treatment, the association between ADRA1A R347C polymorphism and remission/response outcomes was evaluated.

Results Treatment response to mirtazapine was significantly better in T allele carriers than C allele homozygotes after 12 weeks of mirtazapine monotherapy. The percentile decline of HAMD-17 score in T allele carriers was larger than that of C allele homozygotes. ADRA1A R347C genotypes were not significantly associated with remission.

Conclusions The result showed that treatment response to mirtazapine was significantly associated with ADRA1A R347C genetic polymorphism. T allele carriers showed better treatment response than C allele homozygotes. It can be supposed that T allele carriers have a trend of better treatment response to mirtazapine monotherapy.

Key Words Major depressive disorder · Adrenoreceptor alpha 1a · ADRA1A R347C · Mirtazapine · Treatment response.

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Introduction

Major depressive disorder (MDD) is becoming one of the most significantly problematic diseases in the world, with a lifetime prevalence of up to 13%.[1] MDD is characterized by its heterogeneity of etiology involving both genetic and environmental factors.[2] Nowadays, it is widely known that the malfunction of neurotransmitter systems can cause many symptoms of depression. Even though pathophysiology of MDD is still not fully understood, significant evidences show that abnormalities of the norepinephrine (NE) and serotonin (5-HT) neurotransmitter systems are observed in major depressive disorder.[3] Therefore, most of the antidepressants such as selective serotonin reuptake inhibitor (SSRI), serotonin norepinephrine reuptake inhibitors (SNRI) and noradrenergic and specific serotonergic antidepressant (NaSSa) are targeting NE and 5-HT neurotransmitter systems for the improvement of MDD symptoms.

By using these antidepressants, many MDD patients are well treated. However, there is an apparent observation that some patients have tendency to respond to specific pharmacological class, while others respond selectively to another specific pharmacological drug.[4] This difference is thought to be made due to many genetic factors, and for the achievement of individualized treatment that can reduce the nonresponse and side effects, patients' genetic variabilities should considered significantly.

Noradrenergic function is known as one of the keys to solve the pathophysiology of MDD. Especially, brain's adrenoceptors (α1) located in or close to monoamine-containing neuron cell bodies (NE and 5-HT) form epinephrine-innervated α1-adrenergic system that activates behaviors by exciting major monoaminergic systems of the brain, and the function of the system is impaired in patients with MDD.[5] And through indirect α1 adrenorecep-

tor-mediated enhancement of 5-HT neuron firing and blockade of inhibitory α2-adrenergic heteroreceptors located on 5-HT terminals, extracellular 5-HT increases. Therefore, both α1- and α2-adrenergic receptors contribute to the pathophysiology of MDD, and further, the treatment response of patients who receive antidepressants that affect to the noradrenergic system. α1-adrenergic receptor family has three subtypes, α1A, α1B, and α1D and each individual subtype's clear function has yet to be known.[6]

Mirtazapine is a NaSSa which is widely used in MDD treatment, and is considered to be a useful option in patients with MDD.[7] Mirtazapine is a selective antagonist at α2-adrenergic auto- and heteroreceptors which regulate neuronal NE and 5-HT release. Its noradrenergic activation via α2-autoreceptor blockade and the consequent indirect enhancement of serotonergic transmission are the key factors for MDD treatment.[8] Moreover, through various animal[9-11] studies, mirtazapine's action on α1-adrenoreceptor is also observed.

The adrenoreceptor alpha 1a (ADRA1A) gene, which encodes the α1-adrenergic receptor, is located on chromosome 8p21.2 and has an Arg347Cys polymorphism.[12] The genetic view of ADRA1A gene is shown in Fig. 1.[13] The substitution from arginine (Arg) to cysteine (Cys) at the amino acid position 347 can confer a palmitoylation site and may modulate the cellular localization of the protein.[14] ADRA1A is a member of the G-protein-coupled receptor superfamily which mediate actions in sympathetic nervous system by binding endogenous catecholamines, adrenaline and noradrenaline.[15] Currently, ADRA1A gene polymorphisms are known to have significant relationship with hypertension (ADRA1A G2537C),[11] metabolic syndromes including obesity,[15] benign prostate hyperplasia (ADRA1A R492C).[16] ADRA1A gene polymorphism also has close relationship with neuro-psychiatric disorders such as schizophrenia,[17] attention-deficit hyperactivity disorder,[18] fibromyalgia syndrome,[19] and childhood-onset mood disorders.[20]

As mirtazapine is widely known as α2-adrenergic antagonist, most studies are focusing on the ADRA2A gene polymorphism, especially *Msp*I[21] and *Dra*I[22] polymorphism. Other researches focused on various genetic polymorphisms including COMT val-105/158met, MAOA T941G, MAOB A644G, 5-HTTLPR, 5-HTT Intron2 VNTR, and NET.[23]

In a study that explored the relationship between cocaine dependence and ADRA1A R347C polymorphism, patients who were carrying T allele showed greater treatment response on disulfiram.[24] In the same study, the authors focused on cocaine's ability to inhibit reuptake at the dopamine, serotonin and norepinephrine transporters, which is similar to the phenomena that happens in the pathophysiology of MDD and its treatment. As disulfiram is related to the pharmacologic antagonism of α 1a adrenoreceptors, which is similar to that of mirtazapine, we can make a hypothesis that similar conclusion can be made in MDD treatment ; patients who are carrying ADRA1A R347C T allele might show greater treatment response on mirtazapine. However, there was no report about the relationship between ADRA1A R347C gene polymorphisms and MDD treatment response. Therefore, as described above, even though there are many genetic polymorphisms of ADRA1A gene, we mainly focused on the ADRA1A R347C gene polymorphisms.

As described above, ADRA1A genetic polymorphism has close relationship with various neuro-psychiatric disorders including mood disorders. And as mirtazapine also acts on alpha 1-adrenergic receptor and indirectly affects to 5-HT neuron fir-

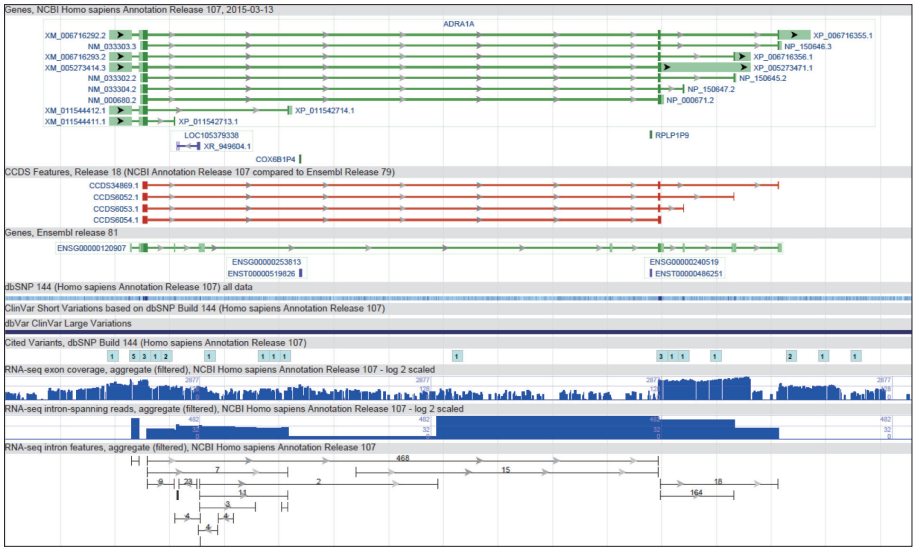

Fig. 1. The genetic view of ADRA1A gene. ADRA1A : adrenoreceptor alpha 1a.

ing, we performed this study to find out the relationship between serotonergic-related polymorphisms in ADRA1A R347C genes and mirtazapine treatment response in Koreans with MDD, and to find out whether ADRA1A R347C gene polymorphism can be the prediction factor for the treatment response.

Methods

Subjects

All subjects, aged from 18 to 81 were recruited from among outpatients visiting the Psychiatric Clinic of Korea University Anam Hospital and gave informed consent to participate in the study. Trained psychiatrists examined all subjects using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorder, fourth edition (DSM-IV) Axis I disorders (SCID-I) and the Korean version of the Diagnostic Interview for Genetic Studies (K-DIGS). The severity of depression was assessed using the 17-item Hamilton Depression Rating (HAMD-17) scale. Only subjects with a score of 18 or higher on the HAMD-17 scale were enrolled.

Patients with primary or comorbid diagnoses of schizophrenia, schizoaffective disorder, bipolar disorder, dementia, clinically relevant personality disorders, and alcohol or substance dependence based on DSM-IV criteria within the previous 6 months were excluded from the study. We also excluded patients with serious or unstable medical illnesses, such as seizures, brain lesions, cardiac problems, pregnancy, liver/kidney failures and abnormal laboratory baseline values. Patients receiving psychotropic medications were subjected to a 2-week washout period. Demographic data, medical history and laboratory data were documented. All subjects were at least 18 years of age. Protocols were approved by the Ethics Committee of the Korea University Medical Center. In accordance with the Declaration of Helsinki, informed consent was given to all subjects who participated in the study.

Clinical assessment

A total of 352 patients were enrolled to the study from November 2009 to March 2012. During the treatment period of this study, all subjects took mirtazapine (Remeron®, Organon®) at a daily dose of 15–60 mg for 12 weeks. Dose titration was done within the usual clinical range, considering patients' initial tolerability and side/adverse effects. For sleep control, 1–2 mg dose of benzodiazepine (lorazepam) was permitted at bedtime. However, psychotropic drugs such as antipsychotics and mood stabilizers were not permitted. Clinical symptoms were evaluated using the HAMD-17 scale and the Clinical Global Impression scale-Severity (CGI-S) at baseline and after 1, 2, 4, 8, and 12 weeks of treatment. The HAMD-17 was performed and managed by a single trained rater, and the rater and genotyper were blinded. Responders were those who showed a ≥ 50% decrease in HAMD-17 score compared to baseline, and remission status were defined by a HAMD-17 total score of 7 points or less.[25]

DNA extraction and genotyping

From each subject, venous blood was drawn in accordance with a protocol approved by the Ethics Committee of the Korea University Medical Center. Genotypes of ADRA1A R347C were analyzed using genomic DNA extracted from peripheral blood mononuclear cells of study subjects by polymerase chain reaction (PCR).

Statistical analysis

Hardy-Weinberg equilibrium for the ADRA1A R347C polymorphisms was tested using a χ^2 test. Genetic associations of the SNP were analyzed using multiple logistic regression and a generalized linear model (GLM) type III for categorical data and continuous variables as appropriate, controlling for age and sex as covariates. A p-value of ≤ 0.05 was regarded as statistically significant. Genetic model assumption for ADRA1A R347C was performed. Codominant, dominant and recessive genetic models were tested assuming the C allele to be associated with a reduced treatment response compared to the T allele : CT genotype patients versus homozygous for T allele and C allele patients (TT, CC genotype patients), C allele carrier patients (CC, CT genotype patients) versus non C allele carrier patients (TT genotype patients), and homozygous for C allele patients (CC genotype patients) versus T allele carrier patients (TT, CT genotype patients). The power to detect associations given the sample size was determined using G · Power ver. 3.1. All statistical analyses were performed using SPSS version 10.0 (SPSS Inc., Chicago, IL, USA).

Results

Clinical characteristics of subjects and Hardy-Weinberg equilibrium for the ADRA1A R347C

Patient data for mean age, age at onset, family history of depression or other mental illness, suicidal attempts are shown in Table 1. No significant differences were found among the three ADRA1A R347C genotypes (CC, CT, TT). HAMD-17 score and CGI-S score at baseline also showed no significant differences among 3 genotypes. The χ^2 test was applied to three genotype frequencies, and the result showed that the subjects were in Hardy-Weinberg equilibrium ($\chi^2 = 3.27$, $p = 0.068$).

Among 352 enrolled patients, total 316 patients completed

Table 1. Demographic characteristics in the MDD treatment group

	ADRA1A R347C genotype (n = 352)			p value
	TT	CT	CC	
n	211	109	32	0.078
Age (year, mean ± SE)	46.22 ± 1.92	45.88 ± 2.95	47.35 ± 5.32	0.946
Sex (male, %)	37 (17.5)	20 (18.3)	3 (9.4)	0.432
Previous history of depression (present, %)	155 (73.5)	76 (69.7)	24 (75)	0.844
Family history of depression (present, %)	32 (15.2)	19 (17.4)	3 (9.4)	0.817
Suicide attempt (present, %)	19 (9.0)	8 (7.3)	1 (3.1)	0.741
Baseline HAMD-17 score (mean ± SE)	20.27 ± 0.38	21.76 ± 0.72	21.52 ± 0.48	0.221
Mirtazapine dosage (mg, mean ± SE)	28.34 ± 2.78	27.97 ± 3.12	28.11 ± 2.34	0.719

ADRA1A : adrenoreceptor alpha 1a, HAMD-17 : 17-item Hamilton Depression Rating

the 12-week treatment trial. 36 patients dropped out of the study due to intolerable adverse effects, economic problems, discontinuation due to symptom improvement, insufficient symptom improvement, and another medical conditions. Intolerable adverse effects included oversedation, GI troubles, dry mouth and significant weight gain. Another medical conditions included diabetes mellitus, cardiovascular diseases, and COPD. These conditions were not related with the use of mirtazapine. To compensate the data missed due to withdrawn patients, last-observation-carried-forward (LOCF) analysis was performed in data of HAMD-17 scores. The clinical characteristics of the withdrawn subjects were not significantly different from the completers, and ADRA1A genotype of the withdrawn subjects did not significantly differ according to dropout reasons.

Association between ADRA1A R347C polymorphism and mirtazapine treatment response

Investigation about the association between ADRA1A R347C polymorphism and mirtazapine treatment response was performed. As shown in Table 2, a significant association of ADRA-1A R347C genotypes and treatment response was found in 12 weeks of mirtazapine treatment. The treatment response to NaSSa antidepressant mirtazapine was better in T allele carriers than the CC homozygote carriers at 12 weeks of treatment [$p = 0.028$, odd ratio = 6.18 (1.21–30.94)]. T allele carriers' proportion in responders was higher than that in non-responders (96.8% vs. 85.5%, respectively). There was no significant difference in treatment response among genotypes in codominant (TT genotype vs. CT genotype vs. CC genotype) and dominant (TT genotype vs. CT and CC genotype) model. The percentile decline of HAMD-17 in patients with the T allele (52.27 ± 2.73%) was significantly larger than that in CC homozygote carriers at 12 weeks of mirtazapine treatment (39.47 ± 8.77%, $p = 0.023$) (Fig. 2). The sensitivity, specificity, positive prediction value and negative prediction value of the T allele was 76.1%, 26.8%, 53.8%, and 46.2%, respectively.

Association between ADRA1A R347C polymorphism and remission status

Inspired by the result that showed the association between ADRA1A R347C polymorphism and mirtazapine treatment response in MDD patients, we also performed the investigation to evaluate the relationship between ADRA1A R347C polymorphism and remission status. However, ADRA1A R347C genotypes were not significantly associated with remission ($p > 0.05$). The result is shown in Table 3. The sensitivity, specificity, positive prediction value, and negative prediction value of T allele was 75.7%, 23.3%, 29.6%, and 70.5%, respectively.

Discussion

Personalized therapy that is able to predict one's treatment response to specific medication is a dream for current medical scientists, and psychiatrists who want to overcome MDD are not the exception. Up to now, many researches about genetic polymorphisms and MDD's treatment response suggest that genetic polymorphisms of adrenergic alpha receptors are closely related to the MDD treatment response to mirtazapine, which is widely-used antidepressant that acts as adrenergic alpha 2 receptor antagonist.[3)8)23)]

However, up to now, the focus of mirtazapine treatment research was mainly on the ADRA2A genetic polymorphisms, as alpha 2 adrenergic receptors directly induces increase of extracellular 5-HT, compared to the indirect method of alpha 1 adrenergic receptors. Although the importance of alpha 1 adrenergic receptors' role is underestimated in the field of MDD treatment, several studies are suggesting that alpha 1 adrenergic receptors and ADRA1A, which encodes the alpha 1 adrenergic receptors, genetic polymorphism is actually related to many psychiatric diseases.[5)9-11)] In an animal study performed by Rogoz et al.,[9)] repeated mirtazapine administration increased the responsiveness of alpha 1-adrenergic system. As both alpha 1 and alpha 2 adrenergic receptors are important in the pathophysiology and treat-

Table 2. Association analysis of ADRA1A R347C with mirtazapine treatment response in patients with MDD

	ADRA1A genotype				Codominant		Dominant		Recessive		ADRA1A R347C allele			p	OR
	TT	CT	CC	Total	p	OR	p	OR	p	OR	T	C	Total		
1 wk, % (n)					0.537	1.24 (0.58−2.63)	0.208	1.87 (0.52−5.44)	0.484	0.39 (0.05−3.92)				0.48	1.27 (0.54−2.86)
Non-responder	63.0 (187)	27.6 (82)	9.4 (28)	100 (297)							76.8 (456)	23.2 (138)	100 (594)		
Responder	43.6 (24)	50.9 (28)	5.5 (3)	100 (55)							69.1 (76)	30.9 (34)	100 (110)		
2 wk, % (n)					0.806	1.04 (0.42−1.92)	0.758	1.09 (0.42−2.48)	0.954	0.01 (0.25−3.92)				0.75	1.03 (0.52−2.04)
Non-responder	65.8 (158)	25.9 (62)	8.3 (20)	100 (240)							78.7 (378)	21.3 (102)	100 (480)		
Responder	47.3 (53)	42.9 (48)	9.8 (11)	100 (112)							72.8 (163)	27.2 (61)	100 (224)		
4 wk, % (n)					0.341	1.22 (0.68−2.37)	0.572	1.19 (0.51−2.62)	0.181	2.97 (0.81−10.84)				0.27	1.38 (0.69−2.61)
Non-responder	62.2 (117)	26.6 (50)	11.2 (21)	100 (188)							75.5 (284)	24.5 (92)	100 (376)		
Responder	57.3 (94)	36.6 (60)	6.1 (10)	100 (164)							79.0 (259)	21.0 (69)	100 (328)		
8 wk, % (n)					0.336	1.28 (0.72−2.43)	0.569	1.25 (0.58−2.69)	0.154	3.38 (1.29−8.34)				0.26	1.36 (0.67−2.59)
Non-responder	62.6 (114)	26.4 (48)	11.0 (20)	100 (182)							75.8 (276)	24.2 (88)	100 (364)		
Responder	56.5 (97)	37.1 (62)	6.5 (11)	100 (170)							77.9 (265)	22.1 (75)	100 (340)		
12 wk, % (n)					0.327	1.31 (0.75−2.49)	0.854	0.98 (0.43−2.10)	0.028	6.18 (1.21−30.94)				0.28	1.34 (0.66−2.56)
Non-responder	60.8 (101)	24.7 (41)	14.5 (24)	100 (166)							73.2 (243)	26.8 (89)	100 (332)		
Responder	59.1 (110)	37.1 (69)	3.8 (7)	100 (186)							76.1 (283)	23.9 (89)	100 (372)		

MDD : major depressive disorder, OR : odds ratio, ADRA1A : adrenoreceptor alpha 1a

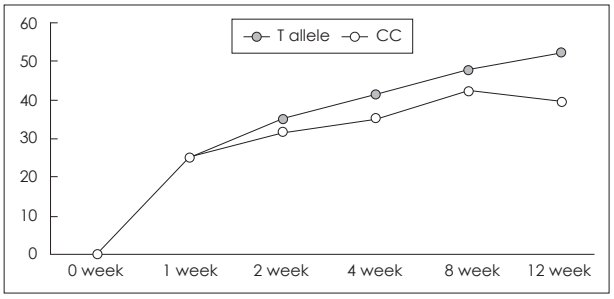

Fig. 2. Percentile decline of HAMD-17 scores with mirtazapine treatment. CC homozygotes vs. T allele carriers. HAMD-17 : 17-item Hamilton Depression Rating.

ment of MDD with mirtazapine, we focused on the ADRA1A R347C genetic polymorphism and mirtazapine treatment response.

To our knowledge, this is the first study that investigated the association between ADRA1A R347C polymorphism and mirtazapine monotherapy, for a period of 12 weeks in single ethnic group of Koreans who were diagnosed with major depressive disorder.

In our study, we found significant association between mirtazapine treatment response and ADRA1A R347C polymorphism of T allele carriers in recessive model. The percentage decline of HAMD-17 score was also significantly larger in ADRA1A R347C T allele carriers. However, we could not find significant correlation between remission status and ADRA1A R347C polymorphism. Through these findings in our study, we can suggest that T allele of ADRA1A R347C polymorphism is a favorable factor in MDD's treatment using mirtazapine. In the analysis of demographic data, no difference of depression history and baseline HAMD-17 score among genotypes was found. Therefore, we could suggest that ADRA1A R347C does not act as a risk factor for MDD development.

Although there is a clear evidence that ADRA1A genetic polymorphism affects significantly to central nervous system and mental disorders (especially schizophrenia),[26-28] only few researches focused on the relationship between the ADRA1A genetic polymorphism and mood disorders. In a study conducted on the Spanish isolate population, Clark et al.[17] reported the result that the ADRA1A genetic polymorphism had significant correlation with the schizoaffective disorder. And in a study conducted on the Hungarian families, Burcescu et al.[20] reported that the adrenergic receptor gene polymorphisms were closely related to the childhood-onset mood disorders.

As the malfunction of alpha 1 adrenoreceptors in the prefrontal cortex under negative situations like severe stress impairs cortical cognitive function[27] and working memory,[29] the ADRA1A genetic polymorphism is known to have association with schizophrenia and schizoaffective disorders. As already known, depression in schizophrenia is quite common, up to 75% in some researches.[30] And in many cases, this depression was related to the disappointment due to lowered working memory and cognitive function.[31]

Therefore, alpha 1a adrenoreceptor plays an important role in MDD by indirect stimulation of 5-HT neuronal firing, and the impairment of alpha 1a adrenoreceptor can lower the cognitive function and working memory and consequently induce depression. Therefore, ADRA1A genetic polymorphism is also have clinically important correlation with mood disorders.

Yet, there is no previous research about the relationship between ADRA1A R347C polymorphism and MDD in Korean population. But several researches showed that the presence of T allele is significantly related with the treatment response of many another neurocognitive disorders. As previously described, the relationship between cocaine dependence treatment response with disulfiram and ADRA1A R347C T allele carriers is known, but as there is no direct evidence that supports the association between cocaine dependence's disulfiram treatment and MDD's mirtazapine treatment, further study should be made in future researches.

Our study has some limitations. First, total number of patients enrolled is relatively low, and the number of C allele homozygotes was especially low. Thus, our results may show difference when similar analysis would be done in larger population group. Second, we investigated only one single SNP of the ADRA1A polymorphism, not all alleleic combinations of ADRA1A polymorphism which can be found in Korean population. Thus, to confirm the association between mirtazapine treatment response and ADRA1A polymorphism, further genetic screening and studies should be performed. Third, as the study selected semi naturalistic design, mirtazapine was titrated to a goal dosage considering treatment responses and intolerable side effects. Finally, multiple testing correction was not performed in this study, and thus cannot ignore the possibility of excessive false positives.

Despite those limitations, this study is showing the possibility that NaSSa antidepressants' treatment response may have association with monoamine transporter gene polymorphisms. And the meaning of this study is that ADRA1A polymorphism, which has been underestimated, can be a favorable factor to predict treatment response of MDD. The result of this study suggests a tendency of better treatment response in T allele carriers.

In conclusion, this study demonstrates that ADRA1A R347C T allele carriers show better treatment response to mirtazapine monotherapy, compared to CC homozygotes, and thus has a

Table 3. Association analysis of ADRA1A R347C with remission to mirtazapine treatment in patients with MDD

	ADRA1A genotype				Codominant		Dominant		Recessive		ADRA1A R347C allele			p	OR
	TT	CT	CC	Total	p	OR	p	OR	p	OR	T	C	Total		
1 wk, % (n)					0.476	1.57 (0.39−6.16)	0.725	1.31 (0.23−6.91)	0.484	−				0.458	1.62 (0.38−6.44)
Non-remitter	62.1 (200)	28.6 (92)	9.3 (30)	100 (322)							76.4 (492)	23.6 (152)	100 (644)		
Remitter	53.3 (16)	46.7 (14)	0.0 (0)	100 (30)							76.7 (46)	23.3 (14)	100 (60)		
2 wk, % (n)					0.248	1.63 (0.62−4.02)	0.511	1.38 (0.43−4.28)	0.999	−				0.216	1.78 (0.62−4.70)
Non-remitter	60.8 (178)	29.0 (85)	10.2 (30)	100 (293)							75.3 (441)	24.7 (145)	100 (586)		
Remitter	64.4 (38)	35.6 (21)	0.0 (0)	100 (59)							82.2 (97)	17.8 (21)	100 (118)		
4 wk, % (n)					0.432	1.23 (0.61−2.47)	0.567	1.28 (0.53−3.08)	0.437	1.97 (0.42−9.83)				0.408	1.36 (0.68−2.76)
Non-remitter	60.8 (155)	29.8 (76)	9.4 (24)	100 (255)							75.7 (386)	24.3 (124)	100 (510)		
Remitter	62.9 (61)	30.9 (30)	6.2 (6)	100 (97)							78.3 (152)	21.7 (42)	100 (194)		
8 wk, % (n)					0.517	1.22 (0.59−2.46)	0.617	1.14 (0.38−2.89)	0.421	2.03 (0.45−9.94)				0.483	1.24 (0.52−2.61)
Non-remitter	61.8 (155)	29.1 (73)	9.2 (23)	100 (251)							76.3 (383)	23.7 (119)	100 (502)		
Remitter	60.4 (61)	32.7 (33)	6.5 (7)	100 (101)							76.7 (155)	23.3 (47)	100 (202)		
12 wk, % (n)					0.608	1.14 (0.54−2.21)	0.854	1.02 (0.41−2.47)	0.403	2.08 (0.51−10.06)				0.586	1.19 (0.51−2.49)
Non-remitter	62.3 (154)	28.8 (71)	8.9 (22)	100 (247)							76.7 (379)	23.3 (115)	100 (494)		
Remitter	59.1 (62)	33.3 (35)	7.6 (8)	100 (105)							75.7 (159)	24.3 (51)	100 (210)		

MDD : major depressive disorder, ADRA1A : adrenoreceptor alpha 1a

promising possibilities to be used as treatment response predictor in MDD treatment.

Conflicts of interest

The authors have no financial conflicts of interest.

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