

Early prediction of blonanserin response in Japanese patients with schizophrenia

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Background: Blonanserin is a second-generation antipsychotic used for the treatment of schizophrenia in Japan and Korea. The present study aimed to examine early prediction of blonanserin in patients with schizophrenia.

Methods: An 8-week, prospective, single-arm, flexible-dose clinical trial of blonanserin in patients with schizophrenia was conducted under real-world conditions. The inclusion criteria were antipsychotic naïve, and first-episode schizophrenia patients or schizophrenia patients with no consumption of any antipsychotic medication for more than 4 weeks before enrollment in this study. The positive predictive value, negative predictive value, sensitivity, specificity, and predictive power were calculated for the response status at week 4 to predict the subsequent response at week 8.

Results: Thirty-seven patients were recruited (56.8% of them had first-episode schizophrenia), and 28 (75.7%) completed the trial. At week 8, blonanserin was associated with a significant improvement in the Positive and Negative Syndrome Scale (PANSS) total score ($P<0.0001$) and in positive ($P<0.0001$), negative ($P<0.0001$), and general subscale scores ($P<0.0001$). In terms of percentage improvement of PANSS total scores from baseline to week 8, 64.9% of patients showed a $\geq 20\%$ reduction in the PANSS total score and 48.6% showed a $\geq 30\%$ reduction. However, 8.1% of patients experienced at least one adverse event. Using the 20% reduction in the PANSS total score at week 4 as a definition of an early response, the negative predictive values for later responses (ie, reductions of ≥ 30 and ≥ 40 in the PANSS total scores) were 88.9% and 94.1%, respectively. The specificities were 80.0% and 51.6%, respectively.

Conclusion: Our results suggest that the blonanserin response at week 4 could predict the later response at week 8.

Keywords: efficacy, safety, antipsychotic

Introduction

Blonanserin was approved in Japan in January 2008 and in Korea in August 2009 for the treatment of schizophrenia (in the People's Republic of China, a Phase III clinical trial has been completed, NCT01516424). Blonanserin is classified as a second-generation antipsychotic (SGA). It has antagonistic activity toward serotonin 2A receptor ($K_i=0.812$ nM), dopamine D₂ receptor ($K_i=0.142$ nM), and dopamine D₃ receptor ($K_i=0.494$ nM) as well as a weak antagonistic activity toward dopamine D₁ receptor ($K_i=1,070$ nM) and adrenergic α_1 receptor ($K_i=26.7$ nM). However, it is almost completely devoid of histamine H₁ ($K_i>100$ nM) and muscarinic M₁ antagonistic activity ($K_i>100$ nM).¹ Blonanserin has a unique pharmacological receptor profile, with higher dopamine D₂ receptor occupancy than other SGAs and lower antagonistic activity toward serotonin 2A receptor than other SGAs.² Our meta-analysis revealed that blonanserin is superior to haloperidol in the improvement of the negative subscale score of the Positive and Negative Syndrome Scale (PANSS).^{3,4} In addition, blonanserin carries a lower risk of hyperprolactinemia

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and weight gain than risperidone.^{4,5} This evidence suggests that blonanserin can be used for the treatment of schizophrenia as a first-line antipsychotic such as aripiprazole.

A recent aripiprazole study involving first-episode psychosis revealed that the response at week 3 of aripiprazole treatment accurately predicts the later response (at week 6).⁶ Nonetheless, no reports have described early prediction of a blonanserin response in patients with schizophrenia. In the present clinical trial, we enrolled patients with first-episode schizophrenia and patients with schizophrenia who did not take any antipsychotic medication for more than 4 weeks before enrollment in this study. Patients with first-episode antipsychotic naïve, schizophrenia are reported to be more sensitive to the adverse effects of antipsychotics than other groups of patients.^{7,8} In addition, several studies^{9,10} have suggested that patients with first-episode schizophrenia respond to low doses of antipsychotic medication.¹¹ Because the blonanserin dose was slowly increased during the present clinical trial, the time point for early prediction of the blonanserin response was set to week 4. Thus, an 8-week, prospective, single-arm, flexible-dose clinical trial of blonanserin in patients with schizophrenia was conducted in real-world clinical settings. We tested whether improvement after the first 4 weeks of treatment can predict the response after 8 weeks.

Materials and methods

Subjects

The present study was conducted from July 2009 to January 2014 at the Fujita Health University Hospital and the Okehazama Hospital. The patients were diagnosed according to the Diagnostic and DSM-IV (*Statistical Manual of Mental Disorders*, Fourth Edition) criteria with a consensus of at least two experienced psychiatrists on the basis of unstructured interviews and a review of all medical records. All subjects met the following inclusion criteria: 1) patients with first-episode schizophrenia and patients with schizophrenia who did not take any antipsychotic medication for more than 4 weeks before enrollment in this study; 2) age 20–70 years; 3) no neurological or systemic disease, including disturbance of hematopoiesis; 4) no history of electroconvulsive therapy within 6 months prior to the study enrollment; 5) absence of pregnancy; and 6) no dependence on any addictive substances other than nicotine in the past 5 years before enrollment. All subjects underwent laboratory blood testing and electrocardiography at the time of enrollment, and no patients were excluded from the study because of a medical problem.

The clinical trial was described in detail to the subjects, and written informed consent was obtained from all participants and their guardians. This study was approved by the Ethics Committees of Fujita Health University and Okehazama Hospital.

Procedures

Because several studies^{9,10} have suggested that patients with first-episode schizophrenia respond to low doses of an antipsychotic,¹¹ all patients received the dose of blonanserin in the range of 4–24 mg/day. The dose of blonanserin was slowly increased (initial dose, 4 mg/day) as a rule unless severe side effects occurred (in such cases, it was slowly decreased). The blonanserin dosage was adjusted at the discretion of a treating psychiatrist. Lorazepam, brotizolam, and biperiden were allowed during our clinical trial (by prescription and for valid clinical reasons).

Evaluation of psychopathology, tolerability, and safety

Patients were tested for psychotic symptoms using PANSS³ at baseline and then again after 4 and 8 weeks. All participants were monitored for adverse events every week by means of full physical examination and general questioning about adverse effects, and the responses were then recorded. All participants underwent blood tests for a complete blood count at week 8 and for liver function, kidney function, electrolytes, prolactin, triglycerides, total cholesterol, and fasting glucose at baseline and at weeks 4 and 8 of the trial.

Statistical analysis

The changes in the PANSS total and subscale scores from baseline to endpoint were evaluated. In addition, the percentage of improvement in the PANSS total score from baseline to week 8 was analyzed (clinical response was defined with increasing stringency, ie, at least 10%, 20%, 30%, or 40% reduction in the PANSS total score) as previous studies.^{12–15} Intent-to-treat analysis was performed using the last observation carried forward (LOCF) method. Subjects who had at least two data points (from the measurements) were entered into study analyses. Each participant's last observation was taken as the endpoint. Paired Student's *t*-test was used to assess statistical significance of the change in psychopathology scores or in laboratory test values from baseline to endpoint. Moreover, the positive predictive value, negative predictive value (NPV), sensitivity, specificity, and predictive power were calculated for the response status at week 4 to predict the subsequent response at week 8.^{12–15} Response

criteria with high NPV and high specificity are particularly useful because clinicians have to quickly change the course of a treatment if the treatment is unlikely to be effective.^{12–15} To determine associations between symptom reductions and the response status, we used chi-square tests. A change in the PANSS total score at week 4 was also examined, as was a change in the PANSS total score at week 8; using regression analysis. All calculations were performed via JMP software (JMP 5.2. 1J, SAS Japan Inc., Tokyo, Japan), and a *P*-value of <0.05 was assumed to denote statistical significance.

Results

Demographics and other characteristics of the patients are presented in Table 1. Thirty-seven patients (56.8% of them had a diagnosis of a first-episode schizophrenia) were eventually recruited, and 28 (75.7%) completed the trial. Nine patients (24.3%) discontinued the study medication at week 4 because of lack of efficacy, adverse effects, or withdrawn consent (Figure 1).

At week 8, blonanserin was associated with a significant improvement in the PANSS total score ($P<0.0001$) and in positive ($P<0.0001$), negative ($P<0.0001$), and general subscale scores ($P<0.0001$) (Table 2). A total of 64.9% of the patients showed a $\geq 20\%$ reduction in the PANSS total score, and 48.6% of the patients showed a $\geq 30\%$ reduction (Figure 2). There were no significant differences in demographic characteristics of the participants between responders and nonresponders (Table 1). Considering a 20% reduction in the PANSS total score at week 4 as a definition of an early response, NPVs for later responses (ie, reductions of ≥ 30 and ≥ 40 in the PANSS total scores) were 88.9% and 94.1%, respectively (Table 3). The specificities were 80.0% and 51.6%, respectively (Table 3). A change in the PANSS total score at week 4 was also associated with that at week 8 in regression analysis ($P<0.0001$, $\beta=0.833$).

Three patients (8.1%) experienced extrapyramidal side effects and akathisia. Two of the three patients discontinued their participation in the study because of the extrapyramidal side effects. No patients had other adverse effects such as weight change, QTc prolongation (on an electrocardiogram), or aberrations in blood tests. Blonanserin nonresponders were more likely to use antiparkinsonian drugs than responders (Table 1).

Discussion

The present study is the first clinical trial examining early prediction of a blonanserin response in patients with

Table 1 Participants' demographics

	Total subjects N=37	Responders: $\geq 20\%$ reduction in PANSS total scores at week 8			Responders: $\geq 30\%$ reduction in PANSS total scores at week 8		
		Responders (n=24)		Non-responders (n=13)	Responders (n=18)		Non-responders (n=19)
		Responders (n=24)	Non-responders (n=13)		Responders (n=18)	Non-responders (n=19)	P-value
Sex (males/females), n (%)	21 (56.8)/16 (43.2)	12 (50.0)/12 (50.0)	9 (69.2)/4 (30.8)	110.3 (13.9)	9 (50.0)/9 (50.0)	12 (63.2)/7 (36.8)	0.419
Outpatients/inpatients, n (%)	8 (21.6)/29 (78.4)	4 (16.7)/20 (83.3)	4 (30.8)/9 (69.2)	29.4 (6.53)	3 (16.7)/15 (83.3)	5 (26.3)/14 (73.7)	0.474
Patients with first episode/others, n (%)	21 (56.8)/16 (43.2)	15 (62.5)	6 (46.2)	26.1 (6.80)	10 (55.6)	11 (57.9)	0.886
Age at the recruitment years, mean (\pm SD)	36.5 (13.2)	35.8 (14.1)	37.6 (11.9)	57.0 (6.89)	37.1 (14.5)	35.8 (12.3)	0.775
PANSS score at the recruitment, mean (\pm SD)	111.1 (21.1)	113.6 (21.6)	106.6 (20.3)	15.4 (7.81)	110.3 (13.9)	111.9 (26.6)	0.826
PANSS total scores	28.6 (7.65)	30.1 (7.19)	25.7 (7.91)	0.0927	29.4 (6.53)	27.7 (8.68)	0.505
PANSS positive subscores	26.5 (6.69)	26.7 (6.77)	26.1 (6.80)	0.802	25.9 (4.75)	27.0 (8.22)	0.620
PANSS negative subscores	56.9 (10.7)	56.9 (12.4)	57.0 (6.89)	0.982	55.4 (10.1)	58.4 (11.4)	0.414
PANSS general subscores	13.4 (7.23)	12.3 (6.87)	15.4 (7.81)	0.227	11.1 (6.66)	15.6 (7.29)	0.0601
Pharmacotherapy at the endpoint	3 (8.1), 3 (0))	0 (0.0)	3 (15.8, 3 (0))	0.0393	0 (0.00)	3 (15.8, 3 (0))	0.0393
Blonanserin dose, mg/day, mean (\pm SD)							
Antiparkinsonian drugs (biperiden), mg/day, n (%), mean (\pm SD))							
Concomitant drugs							
Lorazepam, n (%)	20 (54.1)	13 (54.2)	7 (53.9)	0.985	9 (50.0)	11 (57.9)	0.630
Lorazepam, mg/day, mean (\pm SD)	0.622 (0.681)	0.542 (0.509)	0.769 (0.927)	0.339	0.500 (0.514)	0.737 (0.806)	0.297
Brotizolam, n (%)	23 (62.2)	15 (62.5)	8 (61.5)	0.954	11 (61.1)	12 (63.2)	0.898
Brotizolam, mg/day, mean (\pm SD)	0.243 (0.209)	0.239 (0.219)	0.250 (0.194)	0.890	0.235 (0.225)	0.250 (0.198)	0.841

Abbreviations: PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.

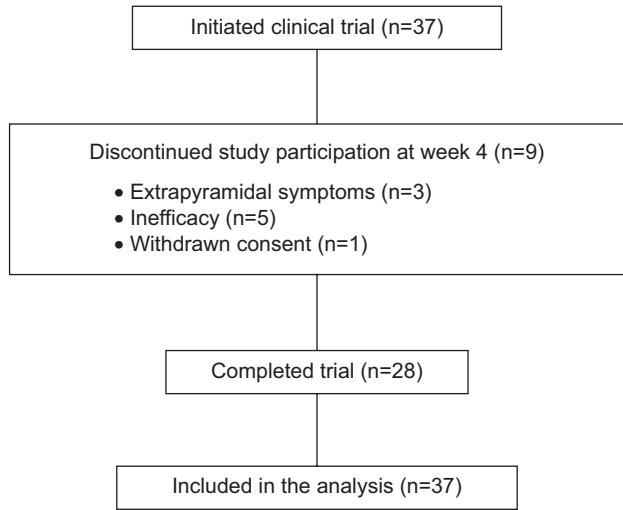


Figure 1 The participants in the study.

schizophrenia. We observed significantly reduced PANSS scores and high response rates as a result of blonanserin treatment in patients with first-episode schizophrenia and in patients with schizophrenia who did not take any prior antipsychotic medication similar to the previous blonanserin study of antipsychotic naïve first-episode schizophrenia.¹ Our present data indicate that blonanserin is well tolerated. Response criteria with high NPV and high specificity are particularly useful because clinicians have to quickly change the course of a treatment if the treatment is unlikely to be effective. When we used the 10% reduction in the PANSS total score at week 4 as a definition of an early response, the specificity of this predictive method was low (Table 3). Nonetheless, when we used a 20% or 30% reduction in the PANSS total score at week 4 as a definition of an early response, then specificity, NPV, and predictive power were high (Table 3). Therefore, if a patient does not show an improved PANSS total score (reduction by >20%) at week 4, the physician should switch from blonanserin to some other antipsychotic. Our results suggest that a blonanserin response after 4 weeks can predict the later

response at week 8. On the other hand, we must note as follows: considering a 10% reduction in the PANSS total score at week 4 as a definition of an early response, positive predictive values for later responses (ie, reductions of >20 and >30 in the PANSS total scores) were 76.7% and 60.0%, respectively.

Other studies showed that improvement of psychopathology after 1, 2, or 3 weeks of antipsychotic treatment can predict the later response to the antipsychotic drug in question (after 6 or 8 weeks).^{12–15} Therefore, the response to treatment of schizophrenia with blonanserin may be predicted as early as 4 weeks into the trial. On the other hand, because we slowly increased the blonanserin dose to ensure the safety of our treatment regimen, we believe that it was rather late in the treatment course when blonanserin reached an optimal dose for the patients. In fact, the mean blonanserin dose at week 2 and 4 was 8.37 (5.20) mg/day [mean (standard deviation)] and 12.5 (7.32) mg/day, respectively.

With regard to the safety of our study protocol, only three patients (8.1%) developed extrapyramidal side effects during this clinical trial, and the incidence of extrapyramidal side effects was lower than that in previous Phase III clinical trials of blonanserin.^{16–19} Nonetheless, three patients (8.1%) received an antiparkinsonian drug during the study. All three received a maximal dose of blonanserin (24 mg/day) because their psychopathological symptoms did not improve after treatment with a moderate dose of blonanserin. Our results suggest that if a patient’s psychopathology does not improve significantly after treatment with a moderate dose of blonanserin for 4 weeks, the treating physician may be able to switch from blonanserin to another antipsychotic before increasing the dose of blonanserin to the maximum in patients with antipsychotic naïve, first-episode schizophrenia with no consumption of any antipsychotic medication for more than 4 weeks.

One of the main limitations of this study is the small sample size. In addition, the clinical trial did not include a

Table 2 Changes from baseline to week 4 and to week 8 in the PANSS total scores and PANSS subscores

	Baseline (n=37)	Mean change at week 4 (n=37) ^a		Mean change at week 8 (n=37) ^b	
	Mean (±SD)	Mean change (±SD)	P-value	Mean change (±SD)	P-value
PANSS total scores	111.1 (21.1)	−25.6 (18.0)	<0.0001	−27.9 (18.2)	<0.0001
PANSS positive subscores	28.6 (7.65)	−8.38 (7.01)	<0.0001	−10.4 (7.22)	<0.0001
PANSS negative subscores	26.5 (6.69)	−5.81 (5.36)	<0.0001	−5.84 (5.93)	<0.0001
PANSS general subscores	56.9 (10.7)	−13.3 (8.03)	<0.0001	−14.4 (8.54)	<0.0001

Notes: ^aNumber of LOCF =0; ^bNumber of LOCF =9 (24.3%).

Abbreviations: LOCF, last observation carried forward; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.

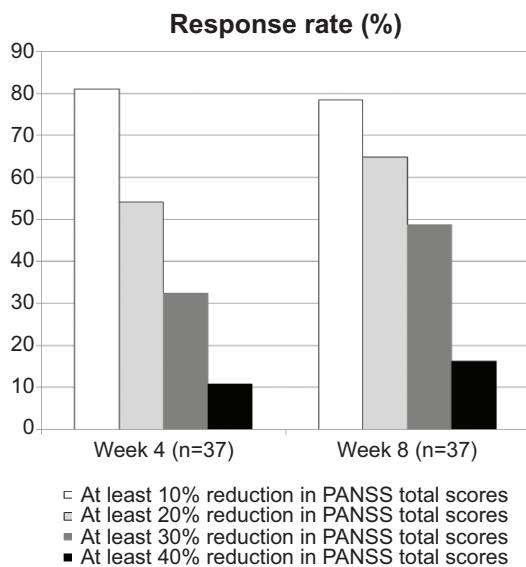


Figure 2 The response rate.

Abbreviation: PANSS, Positive and Negative Syndrome Scale.

control arm of a placebo or active treatment, the trial was not randomized, and the patients and physicians were not blinded to the group assignment of patients. Because of the lack of a control group, the efficacy and tolerability of blonanserin observed in this study cannot be compared with those of other antipsychotic drugs in this population of patients. The Phase III clinical trials of blonanserin^{16–19} did not use the definition of a drug response using PANSS; therefore, we could not compare our results with those of similar studies. Nonetheless, our present study suggests that blonanserin significantly improves psychopathological symptoms. Although the duration of study was short (8 weeks), first-episode schizophrenia patients may often respond slower than multiple-episode patients. Moreover, the current study was not the fixed-dose of blonanserin, and the patients in the study were not tested

for psychotic symptoms using PANSS at 1, 2, and 3 weeks as in the previous studies.^{12–15} Therefore, early prediction of blonanserin response observed in this study cannot be directly compared with other antipsychotic drugs in this population of patients in other studies.^{12–15} Finally, it may not be trivial that intent-to-treat analysis was performed using LOCF method in the study. This method may give a biased estimate of the treatment effect and underestimate the variability of the estimated result.²⁰ It is not clearly justified why this analysis in particular is appropriate and valid.

In conclusion, our findings suggest that blonanserin is effective and well tolerated in patients with first-episode schizophrenia and patients with schizophrenia who did not take any antipsychotic medication for more than 4 weeks before enrollment in this study in Japan. Our results suggest that the response at week 4 of blonanserin predicts the later response (at week 8). Because of the small sample size and the lack of a comparator, a double-blind randomized controlled trial should be conducted to further validate the use of blonanserin for the treatment of schizophrenia.

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Table 3 Conditional probabilities that the response at week 4 will predict the response at week 8 using thresholds for an early response of $\geq 10\%$, $\geq 20\%$, and $\geq 30\%$ improvement in the PANSS total scores and thresholds for later responses of $\geq 20\%$, $\geq 30\%$, and $\geq 40\%$ improvement in the PANSS total score

Improvement at week 4 ^a	$\geq 10\%$ reduction in PANSS total scores			$\geq 20\%$ reduction in PANSS total scores		$\geq 30\%$ reduction in PANSS total scores
	$\geq 20\%$	$\geq 30\%$	$\geq 40\%$	$\geq 30\%$	$\geq 40\%$	$\geq 40\%$
Response criteria at week 8^b						
P-value (χ^2) ^c	0.0019 (9.64)	0.001 (10.9)	0.0957 (2.78)	<0.0001 (18.9)	0.100 (2.70)	0.0044 (8.10)
Positive predictive value, %	76.7	60.0	20.0	80.0	25.0	41.7
Negative predictive value, %	85.7	100	100	88.9	94.1	96.0
Sensitivity, %	95.8	100	100	88.9	83.3	83.3
Specificity, %	46.2	36.8	22.6	80.0	51.6	77.4
Predictive power, %	78.4	67.6	35.1	83.8	56.8	78.4

Notes: ^aImprovements at week 4 are expressed as percentage improvement over the baseline PANSS total scores. ^bResponse criteria at week 8 are expressed as percentage improvement over the baseline PANSS total scores. ^c χ^2 test, $df=1$.

Abbreviation: PANSS, Positive and Negative Syndrome Scale.

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