Table 2. Standardized regression coefficient β and t values for the multiple regression models with the SRS total score in ASD children as the dependent variable. AQ, EQ, and SQ scores in their fathers and mothers were utilized as the independent variables

	β	t
AQ in FA	−0.213	−1.322
AQ in MO	0.567	2.805**
EQ in FA	0.226	1.239
EQ in MO	0.080	0.405
SQ in FA	−0.175	−1.072
SQ in MO	−0.113	−0.735

** $P < 0.01$.
Number of subjects = 44, $R^2 = 0.304$ ($P < 0.05$).
AQ, Autism Quotient; ASD, autism spectrum disorder; EQ, Empathy Quotient; FA, father; MO, mother; SQ, Systemizing Quotient; SRS, Social Responsiveness Scale.

($n = 74$). In the parents of the ASD children (Table 2), the coefficient of multiple determination for multiple regression (i.e., $R^2 = 0.304$) reached significance ($P < 0.05$), and this model revealed that only the AQ total score in the mother was a significant predictor of the SRS score in children (correlation coefficients: $n = 44$, $\beta = 0.567$, $P < 0.01$); the EQ and SQ of the mother and the AQ, EQ and SQ of the father did not reach statistical significance. In the TD parents, the coefficient of multiple determinations for multiple regressions did not reach statistical significance. In the parents of all the children (i.e., TD and ASD) (Table 3), the coefficient of multiple determination for multiple regression (i.e., $R^2 = 0.179$) reached significance ($P < 0.05$), and this model revealed that only the AQ total score in the mother was a significant predictor of the SRS score in children (correlation coefficients: $n = 74$, $\beta = 0.520$, $P < 0.01$); the EQ and SQ of the mother and the AQ, EQ and SQ of the father did not reach statistical significance.

As a complementary analysis, for relationships in which significance was observed in the multiple linear regression analysis, Pearson's correlation coefficients (i.e., simple liner regressions) were calculated between the SRS total score of the children and the AQ total score of their mothers. As shown in Figure 3, a significant positive correlation was observed in the mothers who had ASD children ($r = 0.394$, $P < 0.01$), whereas no significant correlation was found in the mothers who had TD children.

Because there was a significant correlation between the SRS total score and the AQ total score in the ASD group, we added a complementary analysis, that is, a simple correlation analysis using a Pearson correlation coefficient between the five AQ subscales (and total scale) in the mother and the five SRS subscales (and total scale) in their children. As shown in Table 4, there were significant positive correlations in 10 of the 36 correlations.

DISCUSSION

The main aim of this study was to identify phenotypes in mothers and fathers that are specifically associated with the disturbance of social interactions in their young children with ASD in a Japanese sample. This study in a Japanese sample replicates previous findings reported in other countries and provides new evidence. The cross-cultural stability of the AQ and SRS as a measure of the BAP or ASD symptom is the main strength of the study.

This case–control study demonstrated that in two of the five AQ subscales (social skills and communication), the parents of ASD children scored significantly higher than did the parents of TD children, regardless of whether the parent was the mother or the father. The present study replicated four of the five previous studies examining AQ scores in other countries. Bishop *et al.* demonstrated that AQ scores

Table 3. Standardized regression coefficient β and t values for the multiple regression models with the SRS total score in all children (TD and ASD) as the dependent variable. AQ, EQ, and SQ scores in their fathers and mothers were utilized as the independent variables

	β	t
AQ in FA	−0.036	−0.273
AQ in MO	0.520	3.686**
EQ in FA	0.171	1.186
EQ in MO	0.200	1.469
SQ in FA	−0.074	−0.602
SQ in MO	−0.119	−1.026

** $P < 0.01$.
Number of subjects = 74, $R^2 = 0.179$ ($P < 0.05$).
AQ, Autism Quotient; ASD, autism spectrum disorder; EQ, Empathy Quotient; FA, father; MO, mother; SQ, Systemizing Quotient; SRS, Social Responsiveness Scale; TD, typically developing.

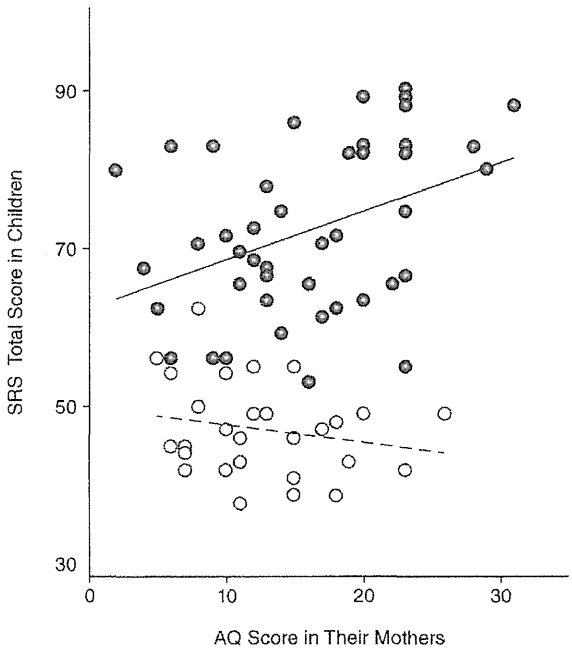

Figure 3. Scatter plot of the Social Responsiveness Scale (SRS) total *T*-score in children and the Autism-spectrum Quotient (AQ) score of their mothers in the (●) autism spectrum disorder (ASD) and (○) typically developing (TD) groups. In the ASD group, the SRS score in children was significantly correlated with the AQ score of their mother ($P < 0.01$). Solid line, regression line for the children with ASD; broken line, regression line for the TD. ASD ($P < 0.01$, $r = 0.394$, $n = 44$); TD ($P = 0.284$, $r = -0.202$, $n = 30$).

differentiate parents of children with an ASD from control parents on the social skills and communication subscales.[11] Ruta *et al.* obtained similar results: the total score and the communication, imagination and social skills subscales of the Italian version of the AQ were higher in ASD parents.[12] Kose *et al.* reported similar results: there were group differences in the AQ total score and in two of the five subscales (i.e. social skills and communication) in the Turkish version of the AQ.[13] In a larger sample size, Wheelwright *et al.* reported that ASD parents scored higher than did the control parents on the total scale and on four of the five AQ subscales (i.e., except the attention to details subscale).[10] Only one study failed to demonstrate differences in the total or AQ subscale scores.[28] Intriguingly, in two of the five studies, a significant group × sex interaction for some AQ subscales was demonstrated with a relatively large sample design.[10,12] Ruta *et al.* reported that the higher scores in parents of ASD children in the imagination subscale were driven by mothers.[12] Wheelwright *et al.* also reported a similar finding for the AQ total score and the imagination and attention-switching subscales.[10] In the present study, as shown in Figure 2, we found the same trend (i.e., higher scores in mothers of ASD children on the imagination and attention-switching subscales); however, we failed to find a significant group × sex interaction. This could be due to the smaller sample size in the present study (i.e., limitation of the statistical power).

For the main aim of this study, as shown in Table 4, we performed a correlation study and provided the first evidence that two of the five autistic traits measured by the AQ subscales (attention-switching and communication) in mothers were

Table 4. Correlation coefficients between AQ subscales in mothers and SRS subscales in their children with ASD

	SRS total	SRS AWA	SRS COG	SRS COM	SRS MOT	SRS MAN
AQ total	0.394**	−0.075	0.383*	0.346*	0.370*	0.375*
AQ: social skill	0.245	0.010	0.179	0.233	0.235	0.205
AQ: attention-switching	0.355*	0.010	0.353*	0.370*	0.262	0.284
AQ: attention to detail	0.089	−0.152	0.199	0.002	0.166	0.118
AQ: communication	0.341*	0.028	0.297	0.292	0.289	0.310*
AQ: imagination	0.212	−0.168	0.188	0.178	0.228	0.284

*$P < 0.05$ and **$P < 0.01$. $n = 44$.
AQ, Autism Quotient; ASD, autism spectrum disorder; AWA, awareness; COG, cognition; COM, communication; MAN, mannerisms; MOT, motivation; SRS, Social Responsiveness Scale.

specifically associated with a disturbance in social ability, as measured by the SRS score, in their young children with ASD. In addition, significant positive correlations in 10 of the 36 correlations were revealed by a Pearson correlation coefficient between the five AQ subscales (and total scale) in the mother and the five SRS subscales (and total scale) in their children. To our knowledge, no previous quantitative study has demonstrated the correlation between the BAP in mothers and the autism phenotype in their children with ASD. However, two case–control studies reported that the higher scores on the imagination[10,12] or attention-switching[10] subscales in parents of ASD children were driven by mothers. Therefore, these findings suggested that the BAP that indexes genetic liability to autism tends to be observed in specific AQ subscales, especially in the case of female subjects.

In the present study, autistic traits measured by the AQ, the EQ and the SQ in fathers were not significantly correlated with disturbances in social ability, measured by the SRS score, in their young children with ASD. Consistent with our results, no previous study has demonstrated a significant correlation between the BAP in the father measured by a self-report questionnaire and severity in their children with ASD. Conversely, many case–control studies have demonstrated that performance in cognitive tasks was lower among the fathers of ASD children than among fathers of TD children.[28–31] We cannot draw a definitive conclusion from our study because we did not measure cognitive function in parents; however, the findings from previous studies suggest that the BAP that indexes genetic liability to autism tends to be observed in cognitive impairment (e.g. executive function or central coherence), but not in the AQ score, especially in male subjects.

This study has some limitations. The first limitation is that the AQ for adults has the format of a self-report questionnaire. Therefore, we need to consider the possibility that the self-report from the parents of ASD children could, in part, reflect their familiarity with the symptoms of ASD. To help rule out a role for response bias on the AQ, future studies are needed to assess how the self-reported traits identified by the AQ relate to behaviors identified using other means of assessment. However, it seems unlikely that such bias could explain the findings that we observed in the present study because the AQ was designed to minimize such biased responding by having test items that ask about an individual's preferences, rather than one's ability or disability.[17] In addition, an individual who has been over-sensitized to autistic behaviors might be expected to score high on all five subscales of the AQ, rather than selectively on two subscales. A second limitation is that we did not measure the intelligence level or the socioeconomic status of the parents; therefore, we could not control for these potential confounds. However, all parents had no prior or current developmental, learning, or behavioral problems, and they were at or above the reading level required to understand these questionnaires. A third limitation is that with our study design, we could not draw a definitive conclusion whether the observed phenotypic correlations between mothers and ASD children were caused by hereditary or environmental factors. Future studies could also include families that have a non-biological child with ASD, to test whether there are effects of environmental factors that contribute to phenotypic correlations between parents and ASD.

Conclusions

In summary, autistic traits in parents were evaluated using the AQ, the EQ and the SQ in 88 parents of children with ASD and in 60 parents of TD children. For the measurement of autistic traits in children, we employed the SRS. In the AQ subscales, the parents of ASD children scored significantly higher than the parents of TD children on two of the five subscale scores, social skills and communication, regardless of whether the parent was a mother or a father. This is the first study in a Japanese sample to demonstrate that the social skills and communication subscales are more sensitive as autism traits. A multiple regression analysis revealed that a higher AQ total score in the mother was only one significant predictor of higher autistic traits (i.e., the SRS total score) in their children, whereas the other total scores in mothers (i.e., the EQ and SQ) and fathers (i.e., the EQ, SQ and AQ) were not significant predictors. A simple linear correlation analysis revealed that two of the five autistic traits measured by the SRS subscales (attention-switching and communication) in mothers were specifically associated with a disturbance in the social ability, measured by the SRS score, in their young children with ASD. Viewing the effects of the BAP on their offspring in this way sheds new light on existing and emerging data and has crucial implications for genetically identifying the BAP in adults.

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Efficacy and safety of aripiprazole once-monthly in Asian patients with schizophrenia: A multicenter, randomized, double-blind, non-inferiority study versus oral aripiprazole

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ABSTRACT

Objective: This study was designed to evaluate efficacy and safety of aripiprazole once-monthly (AOM) by verifying non-inferiority of AOM to oral aripiprazole in Asian patients with schizophrenia.
Method: The study consisted of a screening phase and three phases: an oral conversion phase (≤12 weeks), an oral stabilization phase (≤12 weeks) and a 52-week double-blind phase. Patients meeting stabilization criteria for 4 weeks during the oral stabilization phase were randomly assigned (1:1) to AOM (400 mg) or oral aripiprazole (6–24 mg/day). The primary endpoint was Kaplan–Meier estimated rate of non-exacerbation of psychotic symptoms/non-relapse at Week 26.
Results: A total of 724 patients were screened, and 502 patients entered the oral stabilization phase. Of 455 patients randomized in the double-blind phase, 228 received AOM and 227 received oral aripiprazole. The non-exacerbation of psychotic symptoms/non-relapse rates at Week 26 were 95.0% (AOM) and 94.7% (oral aripiprazole) and the difference was 0.3% (95% CI: −3.9,4.5), thus non-inferiority of AOM compared to oral aripiprazole with respect to non-exacerbation of psychotic symptoms/non-relapse rate was shown with a margin of −3.9% which is well above the pre-defined non-inferiority limit (−15%). The proportions of patients meeting exacerbation of psychotic symptoms/relapse criteria and stabilization of psychotic symptoms/maintenance criteria were 6.6% and 92.5% in both groups. Discontinuation rates due to all reasons were 25.9% (AOM) and 33.5% (oral aripiprazole). AOM was well tolerated as well as oral aripiprazole.
Conclusions: Non-inferiority of AOM to oral aripiprazole was established. AOM is efficacious in maintenance treatment of stabilized schizophrenia, with comparable efficacy and tolerability to oral aripiprazole.
Clinical Trials Registration: JapicCTI-101175

1. Introduction

Schizophrenia is a chronic disease, and maintenance treatment to keep stabilization of symptoms is important as well as acute treatment. In addition, continuation of the medication is essential for relapse prevention. However, adherence to medication is difficult in patients with schizophrenia because of lack of insight, cognitive impairment and drug-related side effects. There are some reports that discontinuation of medication and poor adherence increase risk of relapse or hospitalization (Robinson et al., 1999; Higashi et al., 2013). Long-acting injectable antipsychotics provide the potential for improvement in adherence to medication and reduction of relapse in schizophrenic patients.

Aripiprazole is a second generation antipsychotic with a partial agonism at dopamine D_2 receptors and serotonin 5-HT_{1A} receptors and an antagonism at 5-HT_{2A} receptors (Burris et al., 2002). Aripiprazole is approved for treatment of schizophrenia in more than 65 countries

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including the USA, the EU and Japan. Aripiprazole has demonstrated efficacy in acute and long-term treatment and low incidence of side effects, metabolic side effects, and changes in weight (Kasper et al., 2003; Marder et al., 2003; Potkin et al., 2003). Furthermore, oral aripiprazole has indicated to be effective for prevention of relapse in patients with chronic, stable schizophrenia (Pigott et al., 2003). Thus, aripiprazole is a suitable long-term treatment options for schizophrenia.

Aripiprazole long-acting injectable offers a continuous medication delivery with a favorable dosing interval to maintain symptom stability and prevent relapse as well as rehospitalization. Indeed, aripiprazole once-monthly is approved for maintenance treatment of schizophrenia in the USA, Canada, and the EU. In a phase III study, time to impending relapse was significantly delayed with 400 mg of aripiprazole once-monthly compared with placebo (Kane et al., 2012). In a second phase III study, non-inferiority of aripiprazole once-monthly to oral aripiprazole was demonstrated, and the proportion of patients meeting impending-relapse criteria was significantly higher in patients treated with a sub-therapeutic dose of 50 mg of aripiprazole once-monthly than in patients treated with either 400 mg of aripiprazole once-monthly or oral aripiprazole (Fleischhacker et al., 2014).

The Aripiprazole Long-acting Formulation Psychiatry Asian (ALPHA) study was designed to evaluate efficacy of aripiprazole once-monthly by verifying non-inferiority of aripiprazole once-monthly, the long-acting injectable, to oral aripiprazole as well as assess its safety profile in Asian stabilized patients with schizophrenia. The results of the trial were intended for the regulatory submission of aripiprazole once-monthly for treatment of schizophrenia in Japan.

2. Materials and methods

2.1. Study design

This multicenter, randomized, double-blind, non-inferiority study was conducted at 91 sites in Japan, Malaysia, Taiwan, and the Philippines between July 2010 and June 2013, in accordance with the Declaration of Helsinki. Prior to study entry, written informed consent was obtained from all patients, if required, from legally acceptable representatives.

The study consisted of a screening phase and three phases: an oral conversion phase (phase 1, up to 12 weeks), an oral stabilization phase (phase 2, up to 12 weeks) and a double-blind phase (phase 3, 52 weeks). Eligibility was determined during the screening phase. In the oral conversion phase, patients were switched from other antipsychotic(s) to oral aripiprazole monotherapy (6–24 mg/day, once or twice a day) within 12 weeks. In the oral stabilization phase, patients were stabilized on oral aripiprazole (6–24 mg/day once daily) and stabilization of psychotic symptoms/maintenance for 4 weeks was confirmed. The stabilization criteria were defined as meeting all of the following criteria for 4 consecutive weeks: 1) Outpatient status; 2) Positive and Negative Syndrome Scale (PANSS; 1–7 rating system, Kay et al., 1987) total score ≤80; 3) lack of specific psychotic symptoms on the PANSS, as measured by a score of <4 (moderate) on each of the following items: conceptual disorganization (P2), suspiciousness (P6), hallucinatory behavior (P3), and unusual thought content (G9); 4) Clinical Global Impressions-Severity (CGI-S; Guy, 1976a) score of <4 (moderately ill); and 5) Clinical Global Impressions-Severity of Suicidality (CGI-SS) score of <2 (mildly suicidal) on part 1 and <5 (minimally worsened) on part 2.

Patients meeting stabilization criteria for 4 weeks during the oral stabilization phase were randomized 1:1 to either aripiprazole once-monthly group or oral aripiprazole group using permuted block method according to the instruction of the Interactive Voice Response System or the Interactive Web Response System. In the aripiprazole once-monthly group, aripiprazole once-monthly was administered into the gluteal muscle once every 4 weeks, over 52 weeks (13 times in total) using a double-dummy design. The starting dose of aripiprazole once-monthly was 400 mg in all patients. However, patients could have a single decrease to aripiprazole once-monthly 300 mg and could have their dose increased back to 400 mg, if needed. Placebo tablets were administered once daily, however, for only 2 weeks after the start of the double-blind phase, aripiprazole tablets were concomitantly administered at dose of either 6 or 12 mg/day that corresponded with the dose of oral aripiprazole used at the end of the oral stabilization phase, to maintain the plasma concentration of aripiprazole. That is, 6 mg/day was administered in patients receiving either 6 or 12 mg/day at the end of the oral stabilization phase, and 12 mg/day was used in patients receiving either 18 or 24 mg/day at the end of the oral stabilization phase. The dose range for the oral aripiprazole (6–24 mg/day) is in accordance with the aripiprazole label in Japan.

In the oral aripiprazole group, aripiprazole tablets were orally administered once daily for 52 weeks at the dose administered at the end of the oral stabilization phase. The dose could be reduced once by 6 mg/day from Week 4 and the dose could be increased back to the original dose if needed. Placebo injectable was administered once every 4 weeks.

In the double-blind phase, the treatment allocation code for the administration of the investigational product was double-blind, meaning that the investigators and the subjects did not know whether the treatment group was the aripiprazole once-monthly group or the oral aripiprazole group. The sponsor's trial personnel, such as those involved in monitoring (blinded), data management, or data analysis, did not access to the treatment allocation code during the conduct of the trial. Only the subject enrollment center had access to the treatment allocation code for this trial, only if it is needed in an emergency.

2.2. Patients

2.2.1. Inclusion criteria

Patients eligible for enrollment in the screening phase were required to be 18 years of age or over and met the Diagnostic and Statistical Manual of Mental health Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria for schizophrenia as a diagnosis. Patients were also required to have had a Body Mass Index (BMI) of 18.5–35.0.

Patients in the oral stabilization phase (phase 2) were required to meet any of the following: 1) patients who were able to complete conversion to aripiprazole tablet monotherapy within 12 weeks after the start of phase 1, 2) patients receiving aripiprazole monotherapy at time of informed consent, 3) patients considered to be capable of receiving aripiprazole tablet monotherapy and who had not received any antipsychotics for at least 12 weeks, at time of informed consent. In addition, patients were adjusted appropriately to"prohibited concomitant medications" and "restricted concomitant medications" requirements stipulated in this protocol.

Patients in the double-blind phase (phase 3) were required to meet the stabilization criteria as stated above.

2.2.2. Exclusion criteria

Patients were excluded if they: had a DSM-IV-TR diagnosis other than schizophrenia; had a complication or a history of diabetes, diabetic ketoacidosis, or diabetic coma; had liver, kidney, heart or hematopoietic organ dysfunction; or were lactating or pregnant. In addition, patients were excluded if they had a complication or a history of polydipsia, Parkinson's disease, tardive dyskinesia, neuroleptic malignant syndrome, rhabdomyolysis, paralytic ileus, alcohol dependence or drug abuse, suicide attempt or self-injury, cerebral vascular disorder, convulsive disorders including epilepsy, organic brain disorder, agranulocytosis or granulocytopenia, or other complications. Patients who had received electroconvulsive therapy within 12 weeks prior to informed consent, who had participated in any other clinical trials within 24 weeks prior to informed consent, for whom clozapine had been ineffective or had responded only to clozapine, and who had been

judged by the investigator or subinvestigator to be inappropriate for inclusion in this trial for any other reasons were excluded.

2.3. Assessments

The primary efficacy endpoint was the non-exacerbation of psychotic symptoms/non-relapse rate at Week 26 in the double-blind phase calculated by Kaplan–Meier method. Exacerbation of psychotic symptoms/relapse was defined as meeting any of the following 4 criteria:

1) CGI-I score of ≥5 (minimally worse) and A {an increase on any of 4 individual PANSS items [conceptual disorganization (P2), hallucinatory behavior (P3), suspiciousness (P6), unusual thought content (G9)] to a score of ≥5 (moderate severe) with an absolute increase of ≥2 on that specific item since randomization} or B [an increase on any of those PANSS items to a score of ≥5 (moderate severe) and an absolute increase of ≥4 on the combined score of those items since randomization].
2) Hospitalization due to exacerbation of psychotic symptoms.
3) CGI-SS score of 4 (severely suicidal) or 5 (attempted suicide) on part 1 and/ or 6 (much worse) or 7 (very much worse) on part 2.
4) Violent behavior resulting in clinically significant self-injury, injury to another person, or property damage.

It is reasonable to support that non-exacerbation of psychotic symptoms/non-relapse rate at Week 26 is an endpoint because it was verified that the time to relapse was significantly longer for aripiprazole compared with placebo for 26 weeks (Pigott et al., 2003). When exacerbation of psychotic symptoms/relapse criteria was met during the double-blind phase (52 weeks), the trial was discontinued at that point.

The secondary endpoints were the following items in the double-blind phase: time to exacerbation of psychotic symptoms/relapse, non-exacerbation/non-relapse rate at each time point other than Week 26, mean change in PANSS total score and each subscale total score, proportion of patients meeting exacerbation of psychotic symptoms/relapse criteria, proportion of patients meeting stabilization of psychotic symptoms/maintenance criteria, proportion of patients achieving remission [a score of ≤3 on each of the following specific PANSS items, maintained for a period of 6 months: delusions (P1), conceptual disorganization (P2), hallucinatory behavior (P3), blunted affect (N1), passive/apathetic social withdrawal (N4), lack of spontaneity and flow of conversation (N6), mannerisms and posturing (G5), unusual thought content (G9)], mean change in CGI-S score, mean CGI-I score, and time to discontinuation due to any reason.

In addition, mean change in MOS 36-Item Short-Form Health Survey (SF-36) was used to assess quality of life (Fukuhara et al. 1998a, b).

Safety was evaluated by adverse events (AEs), clinical laboratory tests (including prolactin levels), vital signs, body weight, 12-lead electrocardiography, Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS; Inada, 2009), Abnormal Involuntary Movement Scale (AIMS; Guy, 1976b), Barnes Akathisia Rating Scale (BARS; Barnes, 1989), CGI-SS, Columbia Suicidal Severity Rating Scale (C-SSRS), injection site reaction, and self-assessment of injection site pain [visual analog scale (VAS)].

2.4. Statistical analyses

The primary efficacy sample included all patients who had received at least one dose of double-blind study medication and for whom the post-dosing efficacy parameter data had been obtained. The safety sample included randomized patients who had received at least one dose of double-blind study medication and for whom the post-dosing

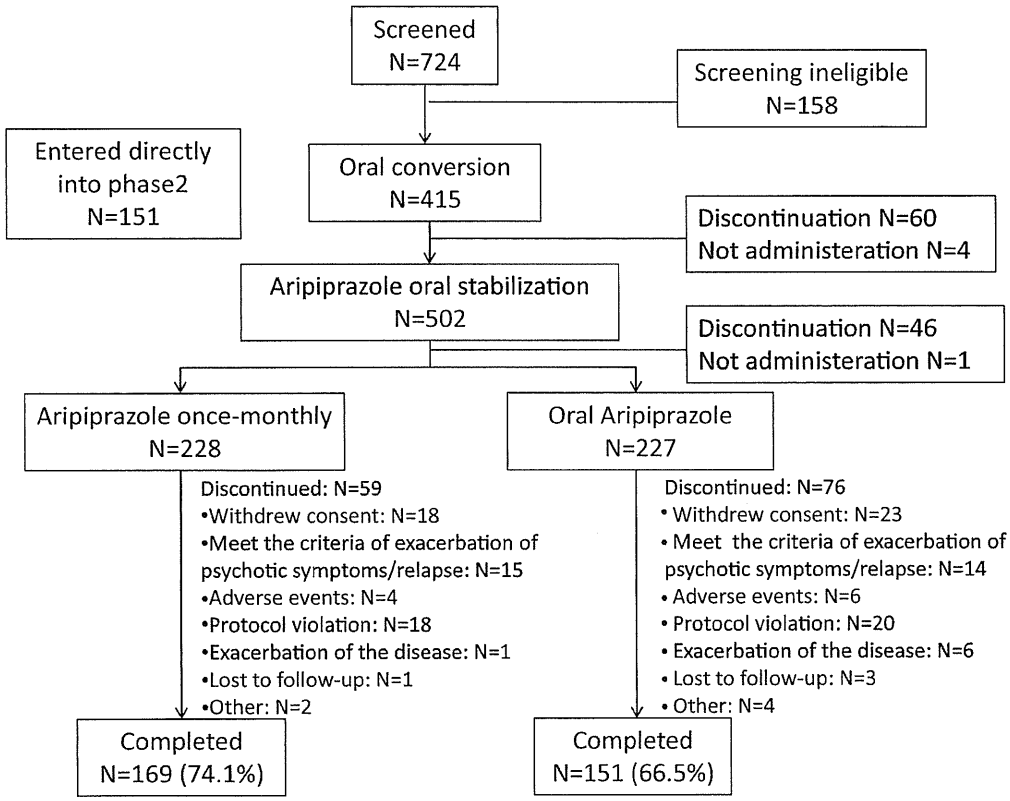

Fig. 1. Patient disposition.

safety parameter had been obtained. Analyses were conducted using LOCF data.

The primary efficacy endpoint in this trial was the non-exacerbation of psychotic symptoms/non-relapse rate at Week 26 in the double-blind phase calculated by the Kaplan–Meier method. The objective of the primary efficacy analysis was to show the non-inferiority of 400 mg of aripiprazole once monthly to oral aripiprazole (6–24 mg), over a 52-week administration period from the start of administration in the double-blind phase, using the non-exacerbation of psychotic symptoms/non-relapse rate at Week 26 calculated by the Kaplan–Meier method as a marker.

In the efficacy sample, the non-exacerbation of psychotic symptoms/non-relapse rate at Week 26 was calculated for each group using the Kaplan–Meier method. The difference (400 mg of aripiprazole once-monthly to 6–24 mg of oral aripiprazole) and the two-sided 95% confidence-interval (CI) of that difference were calculated. When the lower limit of the two-sided 95% CI of that difference was greater than or equal to −15%, 400 mg of aripiprazole once-monthly was judged to be non-inferior to 6–24 mg aripiprazole tablets. The non-inferiority margin was set at 15%, based on the exacerbation rate and non-exacerbation rate in placebo groups and active drug group in the previous studies (Pigott et al., 2003, European Medicines Agency, 2008; Hough et al., 2010).

Regarding the time to exacerbation of psychotic symptoms/relapse, the hazard ratio and the two-sided 95% CI of that ratio were calculated using the Cox proportional hazards model. Changes in PANSS total score, each positive, negative, and general psychopathology subscale scores, and CGI-S were analyzed using analysis of covariance (ANCOVA) model using LOCF dataset, with the treatment group as main effect, and with the baseline of the double-blind phase as a covariate. Mean CGI-I scores at each time point were assessed by the Cochran–Mantel–Haenszel test, based on row mean score statistics.

The 95% CIs of the differences in percentages were calculated for the proportions of patients meeting exacerbation of psychotic symptoms/relapse criteria, patients meeting stabilization of psychotic symptoms/maintenance criteria, and patients achieving remission.

The results of all statistical tests were interpreted at the 5% significance level.

The sample size was calculated as follows: It is assumed that the hazard ratio of aripiprazole once-monthly and oral aripiprazole was the same and remained constant regardless of the time point. The expected dropout rate was 20% at Week 26 due to reasons other than dropout under the definition of exacerbation of psychotic symptoms/relapse, such as withdrawal of consent and discontinuation due to AEs, and the non-exacerbation/non-relapse rate at Week 26 was set at 75% according to the Kaplan–Meier method. A 10,000-time simulation in which there was a ≥90% probability that the lower limit of the two-sided 95% CI for the difference in non-exacerbation of psychotic symptoms/non-relapse rate at Week 26 was equal or exceeded −15% found 410 patients in a randomized population.

3. Results

3.1. Patient disposition

In total, 724 patients were screened, of whom 566 were eligible to enter this study; 415 patients entered the oral conversion phase (phase 1) and 151 patients entered the oral stabilization phase (phase 2) directly. Of 455 patients randomized in the double-blind phase (phase 3), 228 received aripiprazole once monthly and 227 received oral aripiprazole (Fig. 1). Of the randomized patients, 169 (74.1%) in the aripiprazole once-monthly and 151 (66.5%) in oral aripiprazole completed the study. Reasons for treatment discontinuation are provided in Fig. 1.

Baseline demographics and patient characteristics are shown in Table 1 and were similar between groups. All patients were Asian. The majority of patients were from Japan (52.1%), followed by the Philippines (18.9%), Malaysia (18.5%) and Taiwan (10.5%).

Table 1
Baseline demographic and clinical characteristics of randomized patients.

Characteristic		Aripiprazole once-monthly (n = 228)	Oral aripiprazole (n = 227)
		n (%)	n (%)
Gender, male		136 (59.6)	141 (62.1)
Age (years), mean ± SD		40.2 ± 12.6	38.2 ± 10.3
Baseline weight (kg), mean ± SD		65.2 ± 13.1	64.9 ± 12.8
Baseline BMI (kg/m^2), mean ± SD		24.4 ± 4.0	24.1 ± 3.9
Country	Japan	118 (51.8)	119 (52.4)
	Malaysia	43 (18.9)	41 (18.1)
	Philippines	42 (18.4)	44 (19.4)
	Taiwan	25 (11.0)	23 (10.1)
Type DSM-IV-TR	Paranoid type	143 (62.7)	142 (62.6)
	Disorganized type	10 (4.4)	10 (4.4)
	Catatonic type	4 (1.8)	10 (4.4)
	Undifferentiated type	53 (23.2)	45 (19.8)
	Residual type	18 (7.9)	20 (8.8)
Age of first episode (years), mean ± SD		26.5 ± 9.6	26.5 ± 8.6
Time since first episode (mon), mean ± SD		163.3 ± 130.5	139.9 ± 113.2
Baseline severity at the oral stabilization phase, mean ± SD			
PANSS total score		57.6 ± 13.3	56.0 ± 13.3
CGI-S		3.0 ± 0.8	2.8 ± 0.8
Baseline severity at the double-blind phase, mean ± SD			
PANSS total score		54.4 ± 12.4	53.3 ± 12.7
CGI-S		2.8 ± 0.8	2.7 ± 0.8
Final dose of aripiprazole at the oral stabilization phase			
6 mg/day		32 (14.0)	27 (11.9)
12 mg/day		57 (25.0)	87 (38.3)
18 mg/day		66 (28.9)	46 (20.3)
24 mg/day		73 (32.0)	67 (29.5)

3.2. Treatment exposure

At the end of oral stabilization phase, the overall distribution of the final dose of aripiprazole was as follows: 6 mg/day 13.0%, 12 mg/day 31.6%, 18 mg/day 24.6%, and 24 mg/day 30.8%.

Of the patients who received aripiprazole once-monthly (n = 228), 186 patients (81.6%) received at least 7 injections and 168 patients (73.7%) received at least 13 injections. Of the patients who received aripiprazole once-monthly (n = 228), 207 patients (90.8%) started on and continued to receive 400 mg with no change in dose and 19 patients (8.3%) reduced to 300 mg and continued on the lower dose. Mean dose of aripiprazole once-monthly during the double-blind phase was 393.79 ± 21.02 mg (mean ± SD).

Of the patients who received oral aripiprazole (n = 227), 173 patients (76.2%) received oral aripiprazole for more than 26 weeks and 149 patients (65.6%) received oral aripiprazole for 52 weeks. Of the patients who received oral aripiprazole, 210 patients (92.5%) kept the dose of placebo injectable with no change in dose and 16 patients (7.0%) reduced the dose and continued with the lowered dose. The mean dose of oral aripiprazole was 15.69 ± 6.16 mg/day and the mean duration of administration was 279.9 ± 129.4 days.

3.3. Efficacy

The non-exacerbation of psychotic symptoms/non-relapse rate at Week 26 in the double-blind phase calculated by the Kaplan–Meier method was 95.0 ± 1.5% for aripiprazole once-monthly and 94.7 ± 1.6% for oral aripiprazole and the difference was 0.3% (95% CI: −3.9,4.5) (Table 2). Thus, the non-inferiority of aripiprazole once-monthly compared to oral aripiprazole with respect to non-exacerbation of psychotic symptoms/non-relapse rate was shown with a margin of −3.9% which is well above the non-inferiority limit

Table 2
Non-exacerbation of psychotic symptoms/non-relapse rate at Week 26 by the Kaplan–Meier method.

	Non-exacerbation of psychotic symptoms/non-relapse rate, % (SE)	Difference	95% confidence-interval of that difference	Non-inferiority margin
Aripiprazole once-monthly	95.0 (1.5)	0.3	−3.9, 4.5	−15%
Oral aripiprazole	94.7 (1.6)			

of −15% that was pre-defined in the study protocol. The non-exacerbation of psychotic symptoms/non-relapse rate after 26 weeks up to 52 weeks was 92.9–94.5% in aripiprazole once-monthly and 92.3–94.1% in oral aripiprazole and was similar between both groups.

Regarding time to exacerbation of psychotic symptoms/relapse, the hazard ratio between aripiprazole once-monthly and oral aripiprazole using the Cox proportional hazards model was 0.94 (95% CI: 0.46, 1.92) (Fig. 2).

The proportion of patients meeting exacerbation of psychotic symptoms/relapse criteria at the endpoint was 6.6% in both groups, and the proportion of patients meeting stabilization of psychotic symptoms/maintenance criteria at the endpoint was 92.5% and high in both groups. The proportion of patients achieving remission criteria in patients maintained for a period of 6 months was 69.4% (129/186) for aripiprazole once-monthly and 71.1% (123/173) for oral aripiprazole (Table 3).

PANSS total scores (±SE) at baseline during the double-blind phase were 54.4 ± 0.8 in aripiprazole once-monthly and 53.3 ± 0.8 in oral aripiprazole. At Week 52, the mean changes from baseline in PANSS total scores, positive scores, negative scores, and general psychopathology scores were similar between both groups. In addition, the mean changes in CGI-S scores during the double-blind phase were comparable between both groups (0.0 ± 0.1 in aripiprazole once-monthly and −0.1 ± 0.1 in oral aripiprazole) and were stable. The mean CGI-I score at Week 52 was 3.5 ± 0.1 in both groups (Table 4).

Discontinuation rates due to all reasons was 25.9% for aripiprazole once-monthly and 33.5% for oral aripiprazole, and the hazard ratio of aripiprazole once-monthly to oral aripiprazole for time to discontinuation due to all reasons was 0.74 (95% CI: 0.52, 1.03) (Cox proportional hazards model) (Fig. 3).

SF-36 mental component summary and physical component summary (±SE) at baseline were 47.3 ± 0.8 and 49.4 ± 0.6 for aripiprazole once-monthly, respectively, and 47.5 ± 0.8 and 49.9 ± 0.7 for oral aripiprazole, respectively. Mean changes in metal component summary in SF-36 at Week 52 were 0.82 ± 0.60 for aripiprazole once-monthly and 0.38 ± 0.61 for oral aripiprazole (the difference: 0.44, 95% CI: −1.24, 2.12, ANCOVA). Mean changes in physical component summary at Week 52 were 0.23 ± 0.58 for aripiprazole once-monthly and −0.27 ± 0.58 for oral aripiprazole (the difference: 0.50, 95% CI: −1.11, 2.11, ANCOVA).

3.4. Safety and tolerability

3.4.1. Adverse events

During the double-blind phase, 176 (77.2%) patients in the aripiprazole once-monthly group and 180 (79.3%) patients in the oral aripiprazole group experienced at least 1 treatment-emergent adverse event (TEAE). TEAEs with an incidence of at least 5% in either group in the double-blind phase are shown in Table 5. The common AEs in either

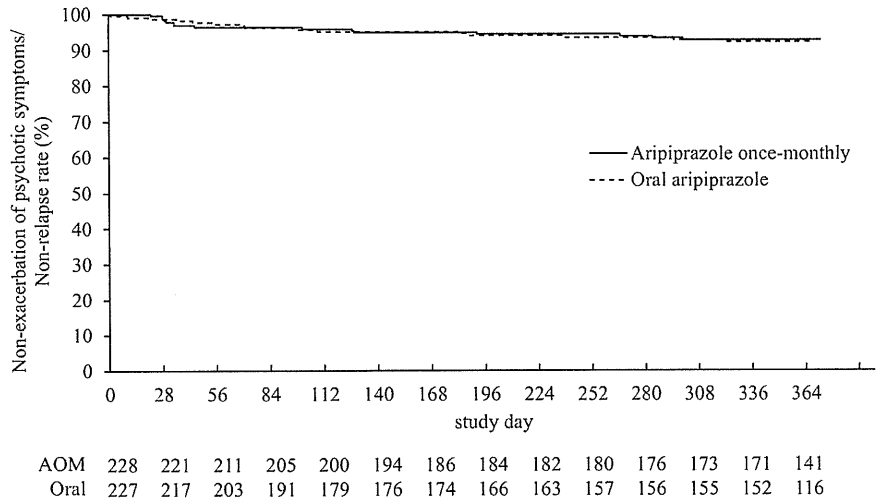

Fig. 2. Time to exacerbation of psychotic symptoms/relapse in double-blind phase calculated by the Kaplan–Meier method. Hazard ratio was 0.94 (95% CI: 0.46, 1.92) (Cox proportional hazard model).

Table 3
Proportion of patients meeting exacerbation of psychotic symptoms/relapse criteria, meeting stabilization of psychotic symptoms/maintenance criteria, and achieving remission criteria.

Proportion of patients	Aripiprazole once-monthly (n = 228)	Oral aripiprazole (n = 227)	95% confidence-interval of the difference
Exacerbation of psychotic symptoms/ relapse	6.6% (n = 15)	6.6% (n = 15)	−4.6, 4.5
Stabilization of psychotic symptoms/maintenance	92.5% (n = 211)	92.5% (n = 210)	−4.8, 4.9
Remission[a]	69.4% (n = 129)	71.1% (n = 123)	−11.2, 7.7

[a] Remission rate in patients who continued treatment for a period of 6 months (Aripiprazole once-monthly; n = 186, oral aripiprazole: n = 173).

Table 4
Mean change in secondary efficacy outcomes in the double-blind phase (LOCF).

Rating scale[a]	Aripiprazole once-monthly (n = 228)	Oral aripiprazole (n = 227)	Difference	(95% CI)
PANSS total score, mean (SE)				
Double-blind baseline	54.4 (0.8)	53.3 (0.8)		
Change to Week 52	−2.3 (0.8)	−2.7 (0.8)	0.4	(−1.8, 2.5)[b]
PANSS positive score, mean (SE)				
Double-blind baseline	11.5 (0.2)	11.4 (0.2)		
Change to Week 52	−0.3 (0.2)	−0.3 (0.2)	0.0	(−0.7, 0.7)[b]
PANSS negative score, mean (SE)				
Double-blind baseline	15.9 (0.3)	15.2 (0.3)		
Change to Week 52	−1.1 (0.2)	−1.0 (0.2)	−0.1	(−0.7, 0.6)[b]
PANSS general score, mean (SE)				
Double-blind baseline	27.0 (0.4)	26.8 (0.4)		
Change to Week 52	−0.9 (0.4)	−1.3 (0.4)	0.4	(−0.7, 1.6)[b]
CGI-S score, mean (SE)				
Double-blind baseline	2.8 (0.1)	2.7 (0.1)		
Change to Week 52	0.0 (0.1)	−0.1 (0.1)	0.0	(−0.1, 0.2)[b]
CGI-I score, mean (SE)				
Change to Week 52	3.5 (0.1)	3.5 (0.1)	0.0	(−0.2, 0.2)[c]

[a] PANSS = Positive and Negative Syndrome Scale; CGI-I = Clinical Global Impression-Improvement; CGI-S = Clinical Global Impression-Severity of illness.
[b] ANCOVA with the score at the baseline of the double blind phase as a covariate and treatment as a factor.
[c] Cochran–Mantel–Haenszel test, based on row mean score statistics.

group were injection-site pain, nasopharyngitis, injection-site erythema, injection-site induration, weight gain, insomnia, akathisia, injection-site dilation, schizophrenia, and diarrhea. The majority of AEs were mild (aripiprazole once-monthly 57.9%, oral aripiprazole 56.4%) or moderate (aripiprazole once-monthly 15.8%, oral aripiprazole 18.1%) in severity. The incidences of side effects by aripiprazole once-monthly and oral aripiprazole were 57% (130/228 patients) and 49.3% (112/227 patients), respectively (Supplementary Table 2). Serious AEs occurred in 13 patients (5.7%) in aripiprazole once-monthly and in 20 patients (8.8%) in oral aripiprazole. The serious AEs reported by ≥2% of patients in either groups were schizophrenia (n = 7, 3.1%) in aripiprazole once-monthly and schizophrenia (n = 8, 3.5%) in oral aripiprazole. Two deaths were reported during the study: 1 patient (cardiac sudden death) receiving aripiprazole once-monthly and 1 patient (head injury) receiving oral aripiprazole.

Table 5
Adverse events occurring during the double-blind phase.

Adverse event	Aripiprazole once-monthly (n = 228)		Oral aripiprazole (n = 227)	
	n	(%)	n	(%)
Injection-site pain	64	(28.1)	43	(18.9)
Nasopharyngitis	55	(24.1)	54	(23.8)
Injection-site erythma	34	(14.9)	22	(9.7)
Injection-site induration	26	(11.4)	11	(4.8)
Weight gain	18	(7.9)	12	(5.3)
Insomnia	17	(7.5)	20	(8.8)
Akathisia	15	(6.6)	14	(6.2)
Injection-site dilation	15	(6.6)	11	(4.8)
Schizophrenia	12	(5.3)	17	(7.5)
Diarrhea	10	(4.4)	15	(6.6)

Occurring at an incidence of ≥5% in either group.

Discontinuation due to AEs in the double-blind treatment phase occurred in 17 patients (7.5%) in aripiprazole once-monthly and 26 patients (11.5%) in oral aripiprazole. AEs resulting in discontinuation that occurred in ≥1% of patients in any group were schizophrenia (n = 11, 4.8%) and unwanted pregnancy (n = 1, 1.1%) in aripiprazole once-monthly and schizophrenia (n = 14, 6.2%), hallucinations (n = 3, 1.3%), and unwanted pregnancy (n = 1, 1.2%) in oral aripiprazole. Patients who experienced AEs leading to dose reduction totaled 16 (7.0%) in aripiprazole once-monthly and 13 (5.7%) in oral aripiprazole, and all did not discontinue after dose reduction.

The numbers of patients with suicidal ideation in aripiprazole once-monthly and oral aripiprazole were 2 (0.9%) and 2 (0.9%) during the double blind phase. There is no significant difference in the proportion of patients with suicidal ideation between aripiprazole once-monthly and oral aripiprazole during the double-blind phase using C-SSRS (0.0–3.1% and 0.0–2.2%). CGI-SS (part 1) and CGI-SS (part 2) were unchanged at 1.0–1.1 and 3.9–4.0, respectively, over 52 weeks in both aripiprazole once-monthly and oral aripiprazole.

3.4.2. Extrapyramidal symptoms

During the double-blind phase, 16.2% of aripiprazole once-monthly and 14.1% of oral aripiprazole patients experienced AEs related to extrapyramidal symptoms. Incidence of akathisia, the most common extrapyramidal symptom, was 5.7% in aripiprazole once-monthly and 6.2% in oral aripiprazole. There was 1 report of tardive dyskinesia in oral aripiprazole. Mean changes in DIEPSS total scores ± SD at Week 52

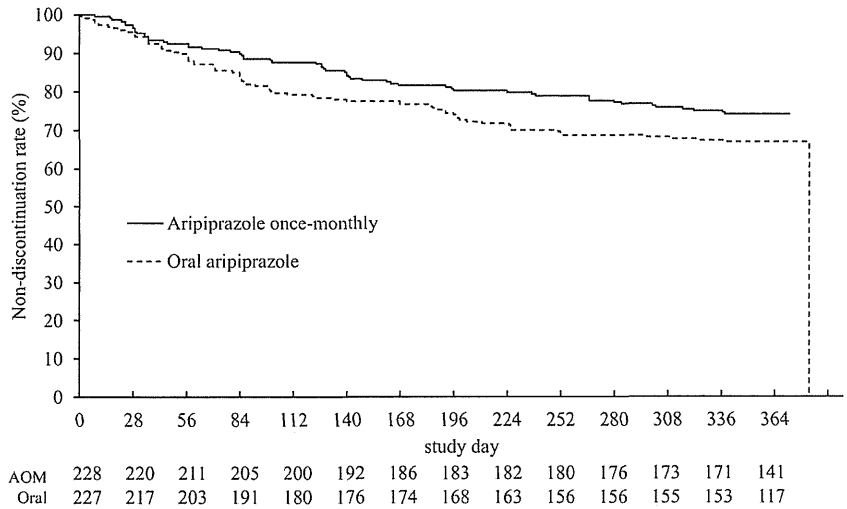

Fig. 3. Time to discontinuation due to all reasons. Hazard ratio of aripiprazole once-monthly to oral aripiprazole was 0.74 (95% CI: 0.52, 1.03) (Cox proportional hazards model).

were −0.2 ± 0.9 (n = 168) in aripiprazole once-monthly and −0.2 ± 0.8 (n = 149) in oral aripiprazole. Mean changes in AIMS total scores at Week 52 were −0.1 ± 0.4 (n = 168) in aripiprazole once-monthly and 0.0 ± 0.5 (n = 149) in oral aripiprazole groups. Regarding akathisia, BARS Global Clinical Assessment of Akathisia scores were 0.1 ± 0.4 (n = 228) at baseline and remained at 0.1 ± 0.3 (n = 168) at Week 52 in aripiprazole once-monthly, and 0.1 ± 0.5 (n = 227) at baseline and remained at 0.1 ± 0.3 (n = 149) at Week 52 in oral aripiprazole. 25% and 23.8% of patients used an anti-parkinsonian drug in aripiprazole once-monthly and oral aripiprazole during the double-blind phase.

3.4.3. Injection-site reaction related adverse events

Of the AEs, the AEs occurring with a greater than 5% difference between aripiprazole once-monthly and oral aripiprazole were injection-site pain, injection-site erythema, and injection-site induration.

Injections of aripiprazole once-monthly were generally well tolerated. There was no discontinuation due to AEs related to injection site reaction in both groups. In self-assessment of injection site pain using the VAS (0–100), mean VAS score after the first injection was 3.5 in aripiprazole once-monthly and 2.5 in oral aripiprazole. Mean VAS scores at the second injection and later were similar in both groups. At the final injection, mean VAS score was 0.8 in aripiprazole once-monthly and 1.6 in oral aripiprazole.

3.4.4. Weight gain and laboratory results

The mean weight changes ± SD during the double-blind phase were 0.87 ± 4.45 kg (n = 168) in aripiprazole once-monthly and 1.44 ± 5.23 kg (n = 149) in oral aripiprazole. The mean and median levels of blood chemistry test items, such as total cholesterol, LDL, HDL, and glucose, were within the normal range in both groups during the double-blind phase (Supplementary Table 3). Mean serum prolactin levels ± SD for aripiprazole once-monthly and oral aripiprazole were 6.8 ± 11.8 ng/mL (n = 228) and 6.8 ± 9.1 ng/mL (n = 227), within the normal range, at baseline and stable within the levels of 5.2–6.0 ng/mL and 5.9–6.3 ng/mL, respectively. Mean changes in prolactin level at Week 52 were −1.6 ± 9.3 ng/mL (n = 167) and −0.5 ± 3.0 ng/mL (n = 149) in aripiprazole once-monthly and oral aripiprazole, respectively.

4. Discussion

This multicenter, randomized, double-blind study proved non-inferiority of aripiprazole once-monthly at 400 mg to oral aripiprazole in Asian patients with schizophrenia, suggesting that aripiprazole once-monthly is effective and exhibit a similar safety/tolerability profile compared to oral aripiprazole. The results of PANSS and CGI evaluation showed that aripiprazole once-monthly as well as oral aripiprazole maintained symptom control in stabilized patients with schizophrenia for 52 weeks. Previous studies reported that oral aripiprazole demonstrated sustained long-term efficacy with favorable safety and tolerability for 52 weeks (Kasper et al., 2003), and relapse prevention in patients with chronic and stable schizophrenia for 26 weeks (Pigott et al., 2003). Aripiprazole once-monthly is non-inferior to oral aripiprazole formulation, which is approved for maintenance treatment of schizophrenia. Therefore, aripiprazole is suitable for long-term treatment in schizophrenia.

In the aripiprazole once-monthly group, relapse rate was 6.6%, and rates of stabilization/maintenance and remission rates in patients who continued for 6 months were high at 92.5% and 69.4%, respectively. Additionally, the rate of discontinuation due to all reasons was lower in the aripiprazole once-monthly group (25.9%) than in oral aripiprazole group (33.5%). These results were similar to the findings of the two previous pivotal studies (Kane et al., 2012, Fleischhacker et al., 2014). The reproducibility of these results may provide support for wider use of aripiprazole once-monthly in clinical practice in Asia and confer a reliable treatment for patients with schizophrenia.

In long-term treatment of antipsychotics, consideration should be given to AEs, such as weight gain, metabolic side effects, and tardive dyskinesia. The incidence of AEs in aripiprazole once-monthly was consistent with that in oral aripiprazole in this study and the previous studies (Kasper et al., 2003; Pigott et al., 2003) and there were no additional unexpected AEs in this study. The incidence of weight gain in aripiprazole once-monthly was low and mean weight change for 52 weeks was less than 1 kg. Akathisia was the most common reported extra pyramidal symptoms-related AEs in the both groups, however, the severity was mainly mild and akathisia was managed successfully by dose reduction and with the addition of an anticholinergic parkinsonian drug.

The incidences of AEs related to injection reaction and pain were higher in aripiprazole once-monthly than in oral aripiprazole. However, the majority was mild in severity, and there was no discontinuation due to AEs related to injection site. Additionally, assessment of injection site pain by patients was similar between both groups from the second injection to the final injection.

The recent meta-analysis of randomized controlled trials of relapse prevention comparing long-acting injectable antipsychotics to oral antipsychotics demonstrated that long-acting injectable antipsychotics were not superior to oral antipsychotics (Kishimoto et al., 2014). On the other hand, a meta-analysis of mirror-image studies, which might reflect real-life clinical practice, showed that long-acting injectable antipsychotics were superior to oral antipsychotics for relapse prevention (Kishimoto et al., 2013). Furthermore, Kirson et al. (2013) reported that long-acting injectable antipsychotics showed advantages in observational studies but no advantages in randomized controlled studies. Thus, study design is an important factor. Our study was designed to verify non-inferiority of aripiprazole once-monthly to oral aripiprazole, and patients received more frequent monitoring and assessments than usual care. Therefore, the patients that participated in this controlled study might show better adherence in oral aripiprazole group.

Some methodological limitations of our study need to be considered. The inclusion of stabilized patients with aripiprazole for 4 weeks and the exclusion of patients with medical comorbidities do not accurately reflect real-world setting. The previous studies included aripiprazole once-monthly 50 mg (a sub-threshold therapeutic dose for assay sensitivity) or placebo (Fleischhacker et al., 2014, Kane et al., 2012), however, the current study does not include either aripiprazole once-monthly at 50 mg or placebo arm.

We demonstrated that non-inferiority of aripiprazole once-monthly compared to oral aripiprazole in this study with a margin of −3.9% which is well above the pre-specified non-inferiority limit of −15%. The results are similar to the finding another study (Fleischhacker et al. 2014). In conclusion, our findings demonstrate that aripiprazole once-monthly at 400 mg is efficacious in maintenance treatment of stabilized patients with schizophrenia, with comparable efficacy and favorable tolerability to oral aripiprazole.

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Contributors

Dr. Ishigooka, Dr. Nakamura, and Mr. Shimizu contributed to interpretation of the data and writing and revision of the manuscript. Dr. Ishigooka, Dr. Nakamura, Dr. Fujii, Dr. Iwata, Dr. Kishimoto, Dr. Iyo, Dr. Uchimura, Dr. Nishimura, and Mr. Shimizu contributed to and have approved the final manuscript.

Conflict of interest

The findings of this study were presented at the 9th Annual Meeting of the Japanese Society of Schizophrenia Research, held in Kyoto, Japan on March 14th, 2014 and at the 29th CINP World Congress, held in Vancouver, Canada on June 23rd, 2014.

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Association between serum levels of glial cell-line derived neurotrophic factor and attention deficits in schizophrenia

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HIGHLIGHTS

- GDNF serum levels did not differ between schizophrenia patients and controls.
- Higher GDNF serum levels were associated with better working memory in controls.
- Higher GDNF serum levels were associated with severe attention deficits in patients.

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ABSTRACT

Several lines of evidence suggest that glial cell-line derived neurotrophic factor (GDNF) plays an important role in the pathophysiology of neuropsychiatric and neurodegenerative disorders. In this study, we investigated the association between GDNF serum levels and the clinical status of medicated patients with schizophrenia. Sixty-three medicated patients with schizophrenia and 52 age- and sex-matched healthy controls were recruited. Patients were evaluated using the brief psychiatry rating scale, the scale for the assessment of negative symptoms (SANS) and neuropsychological tests. Serum levels of GDNF were determined using an ELISA method. Serum levels of GDNF did not differ between schizophrenia patients and controls. Higher GDNF serum levels were associated with better performances on the Digit Span in healthy controls but not in schizophrenics. At the same time, higher GDNF serum levels were associated with severe attention deficits on the SANS subscale, in schizophrenics. Our preliminary study suggests that serum levels of GDNF may be an unsuitable biomarker for schizophrenia, although it may be associated with working memory in healthy controls and the pathophysiology of attention deficits in schizophrenia.

1. Introduction

Schizophrenia is a debilitating psychiatric disorder, primarily characterized by positive symptoms, negative symptoms and cognitive impairment. The latter two symptom clusters are thought to be derived from the prefrontal cortex, and while they share many features, they are separable domains of the illness [8]. Although 75–85% of patients with schizophrenia report cognitive impairment, the underlying pathophysiological mechanisms are still poorly understood, and currently, there are no effective treatments for these impairments [25]. The NIMH project on Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS), established seven cognitive domains, including

Abbreviations: BDNF, brain-derived neurotrophic factor; BPRS, brief psychiatry rating scale; DIEPSS, the drug induced extrapyramidal symptoms scale; DSM-IV, diagnostic and statistical manual of mental disorders-IV; DUP, duration of untreated psychosis; ELISA, enzyme-linked immunosorbent assay; GDNF, glial cell-line derived neurotrophic factor; IQ, intelligence quotient; MATRICS, measurement and treatment research to improve cognition in schizophrenia; NGF, nerve growth factor; PPI, prepulse inhibition; SANS, the scale for the assessment of negative symptoms; WAIS-R, Wechsler adult intelligence scale revised; WCST, the Wisconsin card sorting test.

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working memory and attention, as fundamental cognitive impairments in schizophrenia [16]. Based on this evidence, a growing number of studies have attempted to identify the underlying pathophysiological and pharmacological mechanisms of cognitive impairment in schizophrenia patients.

Current data suggest that neurotrophic factors, such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), play important roles in the pathophysiology of schizophrenia [2]. Glial cell-line derived neurotrophic factor (GDNF) was originally purified from the supernatant of a rat glioma cell line, as a neurotrophic factor for embryonic midbrain dopamine neurons and was later found to have pronounced effects on other neuronal subpopulations [1]. GDNF and its relevant genes are integral to the pathophysiology of neurodegenerative and neuropsychiatric disorders, such as drug addiction [4,7,11], Parkinson's disease [12], Alzheimer's disease [20,22], mood disorders [11,18,23,26,27] and stress vulnerability [24]. Focusing on schizophrenia, no significant association has been reported with GDNF genes [10,11,21], although a study reported nominally positive interaction between GDNF family receptor genes and schizophrenia [21]. However, to date, associations between peripheral GDNF levels and schizophrenia have not been examined.

In this study, we investigated the serum levels of GDNF in patients with chronic schizophrenia and healthy controls, and examined any association with demographic and clinical variables, including cognition.

2. Material and methods

2.1. Study design

The ethics committee of Chiba University Graduate School of Medicine approved the present study. All subjects provided written, informed consent for participation in the study, after the procedure had been fully explained. This study is of an exploratory, cross-sectional and case-control design.

2.2. Participants

Sixty-three Japanese patients with schizophrenia (DSM-IV) were recruited from the outpatient departments of Chiba University Hospital and its affiliated hospitals, in Chiba, Japan. Fifty-two, age- and sex-matched healthy Japanese subjects were recruited as healthy controls. Entry criteria for participants are described in detail elsewhere, and this study used the same sample set as our previous studies [14,15].

2.3. Clinical assessments

Clinical symptoms were assessed using the brief psychiatry rating scale (BPRS) and the scale for the assessment of negative symptoms (SANS). Drug-induced extrapyramidal symptoms were evaluated using the drug induced extrapyramidal symptoms scale (DIEPSS). Intelligence quotient (IQ) scores were estimated using the short version of the Japanese Wechsler adult intelligence scale revised (WAIS-R), which consisted of information, digit span and picture completion subtests. Age at onset, duration of illness, duration of untreated psychosis (DUP) and smoking status were evaluated. The duration of illness subtracting the DUP was used as a partial proxy for cumulative anti-psychotic exposure.

2.4. Cognitive assessments

Cognitive assessment of participants was performed using neuropsychological tests. Details of cognitive assessments and results are available elsewhere [15]. Briefly, participants were assessed using the verbal fluency test (letter, category), the Wisconsin card sorting test (WCST, Keio version) (the number of achieved categories and perseverative errors), the Trail Making Test (Part A and Part B), and the Stroop test (Part D, a list of 24 colored dots; Part C, 24 words naming a color, written in an incongruent color).

2.5. Measurement of GDNF levels from serum

Serum samples were collected from participants between 10:00 and 13:00 h and stored at −80 °C until assayed. Levels of GDNF were measured using a human GDNF ELISA Kit (Promega, Madison, WI, USA). All experiments were performed in duplicate. Protocols were performed according to the manufacturer's instructions, using an acid treatment procedure [17]. The optical density of each well was measured using an automated microplate reader (Emax; Molecular Devices, Sunnyvale, CA, USA).

2.6. Statistical analysis

For comparisons between groups, the χ^2 test was employed for categorical variables, and Student's t-test for continuous variables. Two-way analysis of variance (ANOVA) was employed to examine the effects of diagnosis and gender on serum levels of GDNF. Associations between GDNF serum levels, and clinical and cognitive variables were tested for, using Pearson's correlation coefficients and stepwise multiple regression analysis. Statistical analyses were performed in two-sided tests using SPSS, version 18.0J software (IBM, Tokyo, Japan). The statistical significance was set at $P<0.05$, with power = 0.80. ANOVA with a total of 115 samples enabled us to detect the following effect size: $f=0.26$ (medium-to-large).

3. Results

3.1. Demographic data and clinical variables

Gender, age, education and smoking status did not differ between patients and healthy controls, while the mean estimated IQ in patients was significantly lower than that of healthy controls ($P<0.01$). Furthermore, patients with schizophrenia showed significantly lower scores in all neuropsychological tests ($P<0.05$) [15] (Table 1).

Table 1
Sample characteristics.

	Controls ($n=52$)	Patients ($n=63$)	P
Gender (male/female)	25/27	26/37	NS[a]
Age (years)	34.9 (7.3)	35.9 (8.2)	NS
Education duration (years)	14.7 (2.7)	13.8 (2.3)	NS
Smoking status (no/yes)	43/9	45/18	NS[a]
Estimated IQ	110.2 (12.0)	102.4 (13.9)	<0.01
Age at onset of illness (years)	–	26.8 (7.0)	–
Duration of illness (years)	–	9.1 (7.3)	–
DUP (months)	–	8.1 (13.4)	–
BPRS	–	25.5 (7.5)	–
SANS	–	70.4 (11.8)	–
DIEPSS	–	2.7 (2.7)	–
Antipsychotic dose (mg/day)[#]	–	323.9 (184.2)	–

Values represent mean (SD). NS, not significant.
Abbreviations: DUP, duration of untreated psychosis; BPRS, brief psychiatric rating scale; SANS, scale for the assessment of negative symptoms; DIEPSS, drug induced extra-pyramidal symptoms scale; GDNF, glial cell-line derived neurotrophic factor.
[a] χ^2 test. Other P-values were calculated by Student's t-test.
[#] Chlorpromazine equivalent dose ($n=60$).

Table 2
GDNF Serum levels from inpatients with schizophrenia and healthy controls (pg/mL).

	Controls		Patients		Diagnosis		Gender		Diagnosis × gender	
		n		*n*	*F*	*P*	*F*	*P*	*F*	*P*
Male ($n=51$)	623.2 (220.9)	25	620.2 (247.5)	26	0.08	0.77	3.23	0.075	0.13	0.72
Female ($n=64$)	527.0 (208.0)	27	555.8 (257.9)	37						
Total	573.3 (217.7)	52	582.4 (253.6)	63						

Values represent mean (SD). NS, not significant. Statistical values were calculated by two-way ANOVA.
Abbreviation: GDNF, glial cell-line derived neurotrophic factor.

3.2. Serum GDNF levels

Two-way ANOVA for GDNF serum levels showed no significant effects for diagnosis, gender, or diagnosis x gender interactions (Table 2). Even after adjusting for estimated IQ as a covariate, no significant effect on GDNF serum levels was found ($P>0.05$). In patients with schizophrenia, GDNF serum levels showed no significant differences among the four types of antipsychotic medications, namely, risperidone (628.2 ± 222.2 [mean ± SD, pg/mL], $n=25$); olanzapine (527.1 ± 217.6, $n=18$); aripiprazole (620.7 ± 426.3, $n=9$); and quetiapine (528.4 ± 126.6, $n=8$); ($P=0.38$).

3.3. Association between GDNF serum levels and clinical variables

In the samples, Pearson's correlation coefficients revealed no association between GDNF serum levels, and demographic and cognitive variables (data not shown). In healthy controls, higher serum levels of GDNF were associated with better performances in the Digit Span subtest (Table 3). This association continued to be significant after adjustment for age, gender, education and smoking status, using regression analysis ($\beta=0.40$, $P=0.010$). In patients, higher serum levels of GDNF were positively associated with higher scores of the SANS subscale 5 (attention) (Table 3). As with healthy controls, this association continued to be significant after adjustment for age, gender, education, smoking status and estimated IQ using regression analysis ($\beta=0.35$, $P=0.010$). Serum GDNF levels showed no significant associations with the duration of illness, DUP, cumulative anti-psychotic exposure, and current anti-psychotic drug dose ($P>0.05$).

4. Discussion

Our study demonstrated that GDNF serum levels showed no difference between chronically medicated patients with schizophrenia and healthy controls. Higher serum levels of GDNF were associated with better performances on the digit span in healthy controls, and a greater severity of attention deficits in schizophrenics.

These results imply that GDNF serum levels may be unsuitable as a biomarker for schizophrenia, although previous studies reported its suitability as a potential biomarker for neuropsychiatric and neurodegenerative disorders. In a longitudinal study, Zhang and colleagues reported that during both manic and depressive episodes of bipolar disorder, patients showed lower serum levels of GDNF compared with healthy controls, and that these levels increased to those of healthy controls after eight weeks of pharmacotherapy [26]. A conclusion from this report is that pharmacotherapy may affect GDNF serum levels in patients with bipolar disorder. Indeed, in our study, all the schizophrenic patients had received atypical antipsychotic monotherapy. Therefore, future longitudinal studies that include untreated patients with schizophrenia would provide invaluable new information on this point.

Table 3
Cognitive and clinical data and their correlation coefficients with GDNF serum levels.

	Cognitive and clinical data		Correlation coefficients	
	Controls ($n=52$)	Patients ($n=63$)	Controls	Patients
Estimated IQ	110.2 (12.0)	102.4 (13.9)	0.308*	−0.028
Information	11.1 (2.6)	10.1 (2.7)	0.132	−0.025
Digit span	11.7 (2.9)	10.6 (2.9)	0.370**	0.011
Picture completion	11.0 (1.9)	10.5 (2.2)	−0.036	−0.044
Letter fluency test (words)	35.2 (9.0)	28.0 (8.9)	−0.158	−0.153
Category fluency test (words)	49.1 (6.8)	39.9 (6.9)	−0.137	−0.061
WCST, accomplished categories (n)[a]	4.9 (1.5)	3.3 (2.2)	0.209	−0.030
WCST, perseverative errors (n)[a]	0.9 (1.8)	4.5 (6.7)	0.069	−0.088
Trail making Test A (s)	27.2 (7.7)	33.8 (10.1)	0.065	−0.087
Trail making Test B (s)	52.9 (16.0)	80.5 (27.1)	−0.009	−0.014
Stroop test Part D (s)	12.7 (2.5)	14.2 (2.6)	0.036	−0.021
Stroop test Part C (s)	18.6 (5.3)	22.7 (5.9)	0.138	−0.048
BPRS	–	25.5 (7.5)	–	0.078
SANS	–	70.4 (11.8)	–	0.153
S1 affective flattening	–	16.3 (5.2)	–	0.131
S2 alogia	–	10.4 (3.0)	–	−0.010
S3 avolition apathy	–	15.4 (3.1)	–	−0.023
S4 anhedonia asociality	–	19.1 (3.5)	–	0.083
S5 attention	–	9.3 (3.1)	–	0.305*

Cognitive and clinical data represent mean (SD).
Abbreviations: GDNF, glial cell-line derived neurotrophic factor; WCST, Wisconsin card sorting test; BPRS, brief psychiatric rating scale; SANS, scale for the assessment of negative symptoms.
[a] Spearman's correlation coefficients were calculated for the WCST. Other statistical values represent Pearson's correlation coefficients.
* $P<0.05$.
** $P<0.01$.

Our results suggested that higher GDNF serum levels in healthy controls were associated with better performances in working memory, as measured by the WAIS-R digit span subtest [19]. This finding did not hold for patients with schizophrenia. A previous animal study demonstrated impaired water-maze learning performance in GDNF heterozygous mutant mice, indicative of a role for endogenous GDNF in cognitive abilities [3]. The study may go some way to explain our findings of an association between GDNF serum levels with a subset of cognitive abilities.

By contrast, in schizophrenics, higher GDNF serum levels were associated with a greater severity of attention deficits in schizophrenia. Although in this study attention deficits were categorized as negative symptoms, they could also be considered one of the shared features between cognitive impairment and negative symptoms in schizophrenia [8,16]. A recent animal study demonstrated that administration of BDNF, but not GDNF, into the brain, restored disrupted prepulse inhibition (PPI) in a PPI mouse model [13]. PPI is associated with sensorimotor gating and attention deficits in schizophrenia [5,9]. Therefore, it is unlikely that higher GDNF serum levels would confer a beneficial effect on attention deficits in patients with schizophrenia. Nevertheless, the finding of this study appears contradictory; higher GDNF levels are associated with improved cognitive function in controls, but impaired function in schizophrenics. The effect of anti-psychotic drug treatment might be a plausible explanation for the contradiction, although the precise mechanisms underpinning the association between GDNF serum levels and attention deficits in schizophrenia are yet to be determined.

The source of circulating GDNF in blood is largely unknown, although glia, neuron, kidney and ovary tissues are likely candidates [6]. A strong positive correlation between serum and cerebrospinal fluid (CSF) concentrations of GDNF was reported in healthy controls [22]. If this finding can be confirmed, it is likely that in healthy controls, GDNF serum levels may be associated with GDNF CSF levels, with CSF levels indicative of brain status. To date, it is not known if the same correlation between serum and CSF levels of GDNF exists in schizophrenia.

As with similar studies, this study has a number of limitations, the most prominent being the relatively small sample size. Second, all the patients with schizophrenia were medicated and therefore an effect for medication on GDNF expression could not be ruled out. Third, only a relatively narrow range of cognitive functions were assessed, using typical neuropsychological tests.

In conclusion, our preliminary study suggests that serum levels of GDNF may be unsuitable as a biomarker for schizophrenia, although these levels may be associated with working memory in healthy controls and the pathophysiology of attention deficits in schizophrenia.

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Competing interests

The authors declare that they have no competing interests.

Author contributions

Conception and design: TN, YS and DM. Serum assay, data analysis and drafting of the manuscript: TN. Critical review: YS, DM, ES, KH and MI. All authors approved the final version of this manuscript.

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A prospective comparative study of risperidone long-acting injectable for treatment-resistant schizophrenia with dopamine supersensitivity psychosis

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ABSTRACT

Objective: Dopamine supersensitivity psychosis (DSP) is considered to be one cause of treatment-resistant schizophrenia (TRS). The authors investigated the efficacy of risperidone long-acting injections (RLAI) in patients with TRS and DSP.

Method: This is a multicenter, prospective, 12-month follow-up, observational study that included unstable and severe TRS patients with and without DSP. 115 patients with TRS were recruited and divided into two groups according to the presence or absence of DSP which was judged on the basis of the clinical courses and neurological examinations. RLAI was administered adjunctively once every 2 weeks along with oral antipsychotics. We observed changes in scores for the Brief Psychiatric Rating Scales (BPRS), Clinical Global Impression–Severity of Illness (CGI-S), Global Assessment of Functioning Scale (GAF), and Extrapyramidal Symptom Rating Scale (ESRS) during the study. Of the assessed 94 patients, 61 and 33 were categorized into the DSP and NonDSP groups, respectively.

Results: While baseline BPRS total scores, CGI-S scores and GAF scores did not differ, the ESRS score was significantly higher in the DSP group compared with the NonDSP group. Treatment significantly reduced BPRS total scores and CGI-S scores, and increased GAF scores in both groups, but the magnitudes of change were significantly greater in the DSP group relative to the NonDSP group. ESRS scores were also reduced in the DSP group. Responder rates (≥20% reduction in BPRS total score) were 62.3% in the DSP group and 21.2% in the NonDSP group.

Conclusions: It is suggested that DSP contributes to the etiology of TRS. Atypical antipsychotic drugs in long-acting forms, such as RLAI, can provide beneficial effects for patients with DSP.

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1. Introduction

Antipsychotics are usually effective against the acute symptoms of schizophrenia (Freedman, 2003), especially for the first episode of the

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illness (Lieberman et al., 1993; Szymanski et al., 1996). However, most of the patients relapse into psychotic episodes even after attaining amelioration of their preceding episodes (T.S.S.R. Group, 1992; Robinson et al., 1999). This progressive clinical course is thought to be part of the disease process, indicative of continuing brain dysfunction, while other factors, including effects of the antipsychotic medications being used for treatment, are also thought to play a role in this clinical progression (Zipursky et al., 2013).

Dopamine supersensitivity psychosis (DSP) was first identified in the 1970s (Chouinard et al., 1978), and from 22–43% of all patients with schizophrenia suffer from this psychosis (Chouinard et al., 1988; Chouinard, 1991). The features of DSP include development of tolerance to antipsychotic therapeutic effects, such that even high doses of antipsychotics no longer control symptoms, and an acute exacerbation of symptoms on discontinuing antipsychotics or even after minor stress (Kirkpatrick et al., 1992; Moncrieff, 2006; Chouinard and Chouinard, 2008; Fallon and Dursun, 2011). It is thought that these features may be an integral factor in the development of relapse vulnerability and treatment-resistant psychosis. It has been estimated that more than half of treatment-resistant schizophrenia (TRS) cases may be related to DSP (Iyo et al., 2013). The mechanisms underlying DSP are not fully understood yet, but may be closely associated with the increased density of dopamine D2 receptors (DRD2), which increases behavioral sensitivity to dopamine, following chronic treatment with antipsychotics, as reported in animal models (Inoue et al., 1997; Samaha et al., 2007, 2008; Tadokoro et al., 2012; Iyo et al., 2013). DSP may be also accelerated more profoundly by first-generation antipsychotics than second-generation antipsychotics (Correll et al., 2004; Li et al., 2009; Iyo et al., 2013). Thus, although up-regulation of dopamine D2 receptors (DRD2), induced by antipsychotic therapy blockade, may underlie DSP, an effective treatment strategy for patients with DSP has yet to be established.

We have recently put forward a hypothesis on the mechanisms and treatment strategy for patients with DSP (Iyo et al., 2013). Briefly, optimal DRD2 occupancy by antipsychotics is higher in patients with DSP, leading to the need for higher doses of antipsychotics to achieve a clinical result. However, in these cases, greater quantities of the drug may be eliminated relative to standard doses, as the elimination half-life of the drug may remain the same, independent of the dose load. This greater level of elimination causes drug concentrations to fluctuate across both upper and lower lines of the optimal therapeutic window, particularly for high-dose oral antipsychotics with a relatively short half-life. Furthermore, endogenous dopamine may bind to larger numbers of DRD2, producing enhanced effects. Therefore, in patients with DSP, antipsychotics administered in a form that will yield stable blood concentrations within optimal therapeutic ranges may be of greater use in improving severe and unstable symptoms than the usual tablet formats.

Risperidone long-acting injection (RLAI) was the only long-acting injectable second-generation antipsychotic drug available in Japan at the start of this study. The width between peak and trough blood concentration of RLAI is 32 to 42% smaller than that of oral-risperidone (RIS) using equivalent doses (Eerdenkens et al., 2004). We recently reported that RLAI treatment successfully ameliorated unstable positive symptoms in two DSP cases with TRS (Kimura et al., 2013). Here, we aim to explore the hypothesis that an atypical long-acting agent can prove clinically efficacious in TRS patients with DSP.

2. Methods

2.1. Study design

This is a multicenter, observational study, with a prospective design for assessing clinical outcomes in patients with TRS. The primary objective is to verify the effectiveness of RLAI, that is, the percent change in total BPRS during a 12-month follow-up of the patients. We recruited patients with TRS, who had been selected to receive RLAI by their physicians in clinical setting, from May 2010 to September 2011 and divided them into two groups, defined by the presence or absence of DSP. The assessment of DSP in patients was evaluated by two experienced psychiatrists (H.K. and N.K.). Physicians were given no specific instructions for administering RLAI and oral antipsychotics, although they were instructed to give oral antipsychotics for at least 3 weeks following RLAI initiation and to inject RLAI every two weeks, in accordance with the approved labeling. Physicians were allowed to prescribe antiparkinsonism agents, benzodiazepines and mood stabilizers at their own discretion. Briefly, physicians were encouraged to treat participants so as to achieve maximal clinical effect with minimal side effects. This study was approved by the ethics committees of all participating research facilities. Written informed consent was obtained from all participants after providing them with a full explanation of the study.

2.2. Patients

Patients were eligible for study inclusion if they had a diagnosis of schizophrenia or schizoaffective disorder according to the Structured Clinical Interview for DSM-IV (First et al., 1995). We applied the broad eligibility criteria (Juarez-Reyes et al., 1996) for TRS in the present study, as follows. A patient who scored below 60 in the Global Assessment of Functioning (GAF) at least one year before entering this study and who met either or both of the following two criteria. 1) Non-responder criterion: failure to respond to at least two antipsychotics belonging to two different chemical classes, at dosages equivalent to or greater than 600 mg/day chlorpromazine equivalent (CPZeq) for at least 4 weeks. 2) Intolerance to antipsychotics criterion: TD with moderate or greater severity assessed by ESRS, causing profound distress to the patient. Exclusion criteria for this study were: previous treatment with RLAI and/or clozapine, a history of illegal drug use or substance dependence, the presence of any other AxisIdisorders except for schizophrenia or schizoaffective disorder, mental retardation, pregnancy or any severe physical disease, and the presence of poor medication adherence.

2.3. Measurements

2.3.1. Dopamine supersensitivity psychosis

Presence of DSP was defined using criteria proposed by Chouinard (1991). That is, 1) withdrawal psychosis: acute relapse or exacerbation of psychosis appearing after a dose reduction or discontinuation of antipsychotics, within 6 weeks for oral medication or 3 months for intramuscular medication. This episode must be observed within the last 5 years. Or 2) developing tolerance to antipsychotic effects: This is defined as when an acute relapse or exacerbation of psychosis occurs, independent of a dose reduction or discontinuation of antipsychotic therapy, which cannot be successfully controlled by a 20% increased titration of drug. Or 3) psychotic symptoms which are new to the patient, or of greater severity, occurring immediately after a decrease in drug dosage. Or 4) a history or presence of TD. Based on available information from medical records and hospital staff, if at least one of the listed items above was present, the participant was diagnosed as having a history of DSP. The inter-rater reliability between the two assessors (H.K. and N.K.) was .88. If non identical diagnoses were reached, a consensus-based judgment by these two assessors was applied to the case.

2.3.2. Clinical measurements

The patients were evaluated at baseline (T0), and then after three (T1), six (T2), nine (T3), and twelve months (T4). The primary outcome measure was the percent change in the Brief Psychiatric Rating Scale (BPRS: 18 items, 1–7 scale for each item: Overall and Gorham, 1962) score from T0 to T4. The secondary outcome measures were recorded changes every three months in GAF and Clinical Global Impressions—Severity of Illness (CGI-S). For analyses of patient numbers showing a