表 1: DSP 群と NonDSP 群の背景情報及び臨床症状評価尺度の結果

	DSP 群 (N=106)	NonDSP 群 (N=41)	統計値
年齢（歳）	46.5 [±13.0]	45.5 [±11.1]	N.S.
年齢範囲 （歳）	(19-78)	(22-70)	
性別（男性/女性）	59/47	26/15	N.S.
家族歴（無/F2/F3）	75/21/4	30/8/3	
診断名（統合失調症/統合失調感情障害）	103/3	39/2	N.S.
「治療抵抗性」の該当基準 (反応性不良/耐用性不良/両方)	94/9/3	40/1/0	N.S.
発病年齢（歳）	22.6 [±6.5]	24.4 [±8.6]	N.S.
罹病期間（年）	23.9 [±12.8]	22.3 [±13.1]	N.S.
入院回数	5.1 [±6.2]	3.7 [±3.3]	N.S.
DSP エピソード *リバウンド精神病* *抗精神病薬への耐性* *遅発性ジスキネジア*	 44 59 47	 - - -	
BPRS: 総合点	19.7 [±9.7]	21.0 [±9.9]	N.S.
BPRS: 陽性症状	8.7 [±4.7]	8.8 [±5.4]	N.S.
BPRS: 陰性症状	4.0 [±3.8]	5.1 [±3.6]	N.S.
Deficit 症候群	32	23	P<0.01
GAF	33.3 [±9.6]	33.0 [±10.5]	N.S.
CGI-S	4.9 [±1.0]	4.9 [±1.2]	N.S.
DIEPSS: 総合点	6.8 [±4.8]	4.5 [±3.7]	P<0.01
DIEPSS: 遅発性ジスキネジア	0.88 [±1.17]	0 [±0]	P<0.01

Ⅲ. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
伊豫雅臣	過感受性精神病 治療抵抗性統合失調症の治療・予防法の追求	伊豫雅臣 中込和幸	過感受性精神病 治療抵抗性統合失調症の治療・予防法の追求	星和書店	東京	2013	総ページ 92頁

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Kimura H, Kanahara N, Komatsu N, et al.	A prospective comparative study of risperidone long-acting injectable for treatment-resistant schizophrenia with dopamine supersensitivity psychosis.	Schizophr. Research			2014 *In press.*
Komatsu H, Sekine Y, Okamura N et al.	Effectiveness of information technology aided relapse prevention programme in schizophrenia excluding the effect of user adherence: a randomized controlled trial.	Schizophr. Research	150(1)	240-244.	2013
Kanahara N, Yoshida T, Oda Y et al.	Onset pattern and long-term prognosis in schizophrenia: 10-year longitudinal follow-up study.	PLoS One	8(6)	e67273.	2013
髙瀬正幸, 金原信久, 伊豫雅臣.	非定型抗精神病薬持効性注射剤の可能性：アドヒアランス維持とドパミン過感受性精神病の予防・改善.	臨床精神薬理			2014, *In press.*

金原信久, 鈴木智崇, 伊豫雅臣.	金原信久，鈴木智崇，伊豫雅臣．Clozapineのより具体的な適応症例：治療抵抗性統合失調症の評価に際して.	臨床精神薬理	17(2):	261-275.	2014,
金原信久, 宗岡克政, 木村大, 伊豫雅臣.	非定型持効性注射剤による統合失調症難治例への取り組み.	精神科治療学	29(1)	37-44.	2014

Ⅳ. 研究成果の刊行物・別刷

【Original Article】

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.

Clinical trials registration: UMIN (UMIN000008487)

Keywords: Antipsychotics; Dopamine D2 receptor; Occupancy rate; Tolerance

1. Introduction

Antipsychotics are usually effective against the acute symptoms of schizophrenia (Freedman, 2003), especially for the first episode of the 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 (Robinson et al., 1999; T.S.S.R. Group, 1992). 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., 2012).

Dopamine supersensitivity psychosis (DSP) was first identified in the 1970s (Chouinard, et al., 1978), and from 22-43 percent of all patients with schizophrenia suffer from this psychosis (Chouinard, 1991, 1998). The features of DSP include development of tolerance to antipsychotics 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 (Chouinard and Chouinard, 2008; Fallon and Dursun, 2011; Kirkpatrick et al., 1992; Moncrieff, 2006). 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; Iyo et al., 2013; Samaha et al., 2007, 2008; Tadokoro et al., 2012). 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 antiparkisonism 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 Axis I disorders except for schizophrenia or schizoaffective disorder, mental retardation, pregnancy or any severe physical disease, 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 can not 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 response on BPRS during the study, responders were defined as patients showing a reduction of greater than 20% from baseline. Extrapyramidal symptoms (EPS) were evaluated using the Extrapyramidal Symptom Rating Scale (ESRS: 0-257 point that is summed from all of the factors including the last four sections of clinical impressions: Chouinard and Margolese, 2005). Compliance with treatment medication was monitored using by both a self-rating visual analogue scale for patient and objective observation by their respective physicians, which rated medication administration from 0 to 100% (Garfield et al., 2011). If these measurements differed from each other by no more than 25%, the mean of both values was used as the patient's adherence rate. To reliably evaluate with these measurements, physicians on the study underwent several rounds of assessment training.

2.4. Statistical analysis

All analyses were conducted using SPSS, version 19.0 (IBM, NY, US). Data analyses were conducted on an intent-to-treat basis including all dropout cases (**Figure 1**). Analyses for the primary efficacy measure were performed using a mixed-effects model repeated-measures analysis (Gueorguieva and Krystal., 2004). Treatment group, time

and each time-by-group interaction were included as fixed effects, while baseline scale scores and age were included as covariates. The within-subject factor was considered as a random effect. Compound symmetry was used.

Logistic regression analyses was also performed to look at the effect of treatment group on the outcome measure of treatment response or nonresponse at T4, with age, sex, duration of illness, baseline BPRS and ESRS scores, treatment adherence and the presence or absence of DSP included as items. Continuous and categorical variables were compared by independent t test and chi-square test, respectively. A P value of .05 was set as the threshold of significance.

3. Results

3.1. Patient characteristics and analysis of drop-out cases

Of the 115 patients screened, 21 patients were excluded due to meeting exclusion criteria, being lost to follow-up or refusing to participate before the evaluation for DSP, yielding a final analytic sample of 94 patients (**Figure 1**: DSP group: N=61, NonDSP group: N=33).

Baseline demographics and clinical characteristics were similar between the two groups (**Table 1**). The BPRS positive symptoms score showed no difference between

the two groups, whereas the BPRS negative symptoms score and ESRS score in the DSP group were significantly higher than those of the NonDSP group (P< .001). A total of 75 patients (79.8%) completed the 12-month RLAI treatment. There was no significant difference in the dropout rates between the two groups: 14.8% (N=9) in the DSP group and 30.3% (N=10) in the NonDSP group (P> .05). Seven DSP and 7 NonDSP patients left the study due to an exacerbation of psychotic symptoms. Two DSP patients discontinued due to dystonia and akathisia, and 3 NonDSP patients discontinued due to constipation, hyperglycemia and dystonia.

3.2. Treatment with RLAI and other oral antipsychotics, medication adherence

The mean daily total CPZeq-dose of oral antipsychotics at baseline was about 1000 mg in both groups (**Table 1**). The subjects received quite variable types and combinations of antipsychotics with variable dose ranges. The primary types of antipsychotics used in the present patients were risperidone (1-18 mg), olanzapine (4-40 mg) and quetiapine (200-825 mg). Percent rate of RLAI patients receiving dose of 25mg, 37.5mg and 50mg at T4 was 13.5%, 19.2% and 67.3% respectively in the DSP group, and 13.0%, 21.7% and 65.2% respectively in the NonDSP group. For daily oral antipsychotics dosing (CPZeq-dose), the mean (±SD) doses at T4 were 605 (791) mg/day and 471 (421)

mg/day in the DSP group and the NonDSP group, respectively. There was a significant main effect for Time ($F=9.70$, $P< .001$), but no main effect for Group ($F=0.37$, $P> .05$) or for an interaction of Time × Group ($F=0.07$, $P> .05$). There was no significant difference in the total amount of daily oral antipsychotics and RLAI dose (CPZeq), at T4, between the two groups nor were there significant time effects during the treatment between the groups (**Table 2**).

Mood stabilizers were prescribed for 19 of 61 DSP patients and 14 of 33 NonDSP patients. Among them, 13 DSP patients and 9 NonDSP patients took sodium valproate at T0: their distributions and their mean doses did not differ between the two groups. These doses tended to be lower during the study, though not significantly, in both groups (data not shown). Regarding benzodiazepine and antiparkinsonism agents, neither groups showed any significant differences in baseline doses or in dose changes between T0 and T4.

Adherence to treatment medication, which was measured by a self-administered visual analogue scale at T0, T2 and T4, was 89.2%, 92.2% and 90.0% in the DSP group and 80.6%, 86.8% and 88.4% in the NonDSP group, respectively (**Table 1**). The difference between the self-administered visual analogue scale by each patient and assessment of medication adherence rate by his/her physician was within 25% in all