ORIGINAL RESEARCH

Combination treatment with risperidone long-acting injection and psychoeducational approaches for preventing relapse in schizophrenia

Yueren Zhao[1–3]
Taro Kishi[1]
Nakao Iwata[1]
Manabu Ikeda[3,4]

[1]Department of Psychiatry, Fujita Health University School of Medicine, Toyoake, Aichi, Japan; [2]Department of Psychiatry, Okehazama Hospital Fujita Kokoro Care Center, Toyoake, Aichi, Japan; [3]Department of Neuropsychiatry, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Kumamoto, Japan; [4]Department of Neuropsychiatry, Faculty of Life Sciences, Kumamoto University, Kumamoto, Kumamoto, Japan

Correspondence: Yueren Zhao
Department of Psychiatry, Fujita Health University School of Medicine, Toyoake, Aichi 470-1192, Japan
Tel +81 562 93 9250
Fax +81 562 93 1831
Email zhao@fastmail.jp

Abstract: A recent meta-analysis showed that long-acting injectable (LAI) antipsychotics were not superior to oral antipsychotics for preventing relapse in patients with schizophrenia. We therefore designed a treatment strategy combining risperidone LAI and COMPASS (COMprehensive Psycho-educational Approach and Scheme Set), an original psychoeducational program supporting treatment with risperidone LAI and evaluating subjective treatment satisfaction, transition of symptoms, and effectiveness in preventing symptomatic relapse. The aim of this study was to examine whether addition of COMPASS to risperidone LAI was more effective in preventing relapse in schizophrenia patients than risperidone LAI alone, with the latter group consisting of patients enrolled in a Phase III trial of risperidone LAI in Japan. Patients were followed up for 6 months, with COMPASS continuously implemented from the transition to the observation phase. The primary efficacy measurements were relapse rate (rates of rehospitalization and discontinuation due to inefficacy). Secondary efficacy measurements were the Brief Psychiatric Rating Scale (BPRS) and Global Assessment of Functioning (GAF) scores. Of the 96 patients originally enrolled, 19 (19.8%) were discontinued from all causes. During the 6-month study period, ten of the 96 patients (10.4%) relapsed, compared with a 12.2% relapse rate in patients enrolled in a Phase III trial of risperidone LAI in Japan. Patients showed significant improvements in BPRS total scores ($P = 0.0031$), BPRS positive ($P = 0.0451$), BRPS negative ($P < 0.0001$), and general subscale scores ($P = 0.0031$), and GAF ($P < 0.0001$) from baseline to 6 months. In conclusion, the lower relapse rate observed in patients treated with COMPASS plus risperidone LAI than in patients treated with risperidone LAI alone suggests that COMPASS may have benefits in the treatment of schizophrenia, indicating a need for randomized, controlled trials in larger numbers of patients.

Keywords: adherence, risperidone long-acting injection, psychoeducation, schizophrenia

Introduction

Because schizophrenia is a long-term and recurrent illness, patient adherence to therapy is essential. A survey of 13,000 patients with schizophrenia indicated that the most common reasons for failing to take medication included poor insight (74%), forgetting to take medication (68%), and previous discontinuation of medication (67%) (www.nlm.nih.gov). Poor adherence to treatment can reduce efficacy and contribute to the development of treatment resistance.[1]

Long-acting injections (LAIs) of antipsychotics may overcome poor adherence with oral antipsychotic regimens and reduce the relapse rate. A recent meta-analysis, however, showed that LAIs did not reduce relapse compared with oral antipsychotics in patients with schizophrenia.[2] We therefore developed COMPASS (COMprehensive

Psycho-educational Approach and Scheme Set), a new packaged treatment strategy that combines monotherapy with risperidone LAI and an original psychoeducational program dedicated to supporting treatment with risperidone LAI and evaluated by determining subjective satisfaction with treatment, transition of symptoms, and effectiveness in preventing symptomatic relapse.[3] The aim of this study was to examine whether COMPASS could reduce relapse rates in Japanese patients with schizophrenia receiving risperidone LAI.

Materials and methods
Subjects
The study was conducted from September 2009 to September 2010 in one university hospital (Fujita Health University) and 12 psychiatric hospitals (Okehazama Hospital Fujita Kokoro Care Center, Jindai Hospital, Mikawa Hospital, Kitabayashi Hospital, Kyowa Hospital, Holy Cross Hospital, Tado Ayame Hospital, Matsusaka Kosei Hospital, Kokubu Hospital, Yuge Hospital, Yatsushiro Kosei Hospital, and Meisei Hospital). All procedures followed the clinical study guidelines of the ethics committee of Fujita Health University, Jindai Hospital, Toyota Memorial Hospital, and Okehazama Hospital, and were approved by the internal review board of each hospital. Patients were included if they: had been diagnosed with schizophrenia or schizoaffective disorder, based on International Classification of Diseases (ICD)-10 F2 criteria; were aged 20–70 years; had no systemic or neurologic diseases, including disturbances of hematopoiesis; had no history of electroconvulsive therapy within 6 months prior to study enrollment; were not pregnant; were not dependent on any substances other than nicotine during the 5 years before enrollment; and could not be switched to risperidone LAI monotherapy. No patient was excluded from the study because of a medical condition at baseline.

A complete description of all procedures was provided to the patients. Patients were informed of the goal of treatment (return to everyday life with biweekly administration of risperidone LAI), the need for coadministration of oral medication during the first 4 weeks after initiation of risperidone LAI, and that the potential risk of adverse events with risperidone LAI was similar to that of oral risperidone. Each patient was informed of the costs of risperidone LAI and of other important information, and each provided their written informed consent.

Risperidone LAI and other medications
The initial dose of risperidone LAI was set at 25 mg every 2 weeks. All previous medications were gradually decreased over 3–4 weeks and then discontinued, after which the risperidone LAI dose was increased to 37.5 mg or 50 mg every 2 weeks. All patients visited the relevant study sites every 2 weeks during the study period. Antipsychotics, up to a chlorpromazine equivalent dosage of 100 mg/day, anxiolytics, and hypnotics were allowed for the treatment of restlessness and severe insomnia,[4] and patients were allowed to continue on previously described mood stabilizers and antidepressants. However, concurrent administration of other antipsychotics, mood stabilizers, and antidepressants was not permitted.

Assessments
The primary efficacy measure was relapse rate, defined as the rate of rehospitalization plus the rate of discontinuation due to inefficacy. The secondary efficacy measures included discontinuation rate, scores on the Brief Psychiatric Rating Scale (BPRS)[5] and BPRS subscales,[6] and Global Assessment of Functioning (GAF) score.[7] The BPRS positive score included the item scores for conceptual disorganization, grandiosity, hostility, suspiciousness, hallucinations, and excitement. The BPRS negative score included the item scores for emotional withdrawal and blunted affect. The BPRS general psychopathology score included item scores for somatic concern, anxiety, guilt feelings, tension, mannerisms and posturing, depressed mood, motor retardation, uncooperativeness, unusual thought content, and disorientation. Extrapyramidal symptoms were evaluated using the Drug Induced Extra-Pyramidal Symptoms Scale.[8] Each scale was rated by senior psychiatrists at baseline and after 3 and 6 months.

Overview of original psychoeducational text
Psychoeducation was implemented in all study subjects using the original psychoeducational text, COMPASS (Japanese Original Version: http://bit.ly/COMPASS_JP; English Version: http://bit.ly/COMPASS_EN), beginning at the time risperidone LAI treatment was initiated. COMPASS consists of various components based on three phases, ie, the acute phase, recovery phase, and preparation phase for hospital discharge. Patients had to complete chapter 1 before starting risperidone LAI monotherapy. The speed at which each patient learned chapters 2 and 3 was adjusted by the clinician based on the understanding of each patient, enabling patients to complete every chapter.

Chapter 1 addresses the acute phase of the disease. Patients learn about disease notification, symptoms (positive and negative symptoms, cognitive dysfunction), the characteristics of conventional treatment (oral medication),

and risperidone LAI treatment. It is important for patients to understand their treatments and have proper knowledge about schizophrenia, including the critical period hypothesis.[9] The chapter emphasizes the ability of risperidone LAI treatment to prevent relapse.

Chapter 2 addresses the recovery phase of the disease. Patients learn about self-awareness of their physical condition, including symptoms of schizophrenia and treatment-related adverse events; mental condition, including self-assessment for screening of depression; and how to cope with stress that can trigger symptomatic relapse and worsening of symptoms. The chapter emphasizes the importance for patients of talking about their mental and physical conditions and actions to be taken to cope with stress, as well as the importance of dialogue with other individuals.

Chapter 3 addresses the preparation phase for hospital discharge. Patients review the advantages and disadvantages of treatment with risperidone LAI, learn about social resources that can support their daily life in the community, and are given advice about how they can participate in their community in a concrete manner. Talking and describing their dreams and hopes in their own words is highly prioritized.

Statistical analysis

An intent-to-treat analysis was performed using the last observation carried forward method. Paired Student's t-tests were used to assess the significance of changes in all scores from baseline to endpoint. All statistical analyses were performed using JMP (JMP 5.0.1 J, SAS Japan Inc, Tokyo, Japan), with a P-value < 0.05 considered to be statistically significant.

Results

Ninety-six patients were enrolled in this study, comprising 44 women and 52 men, of mean age 45.4 ± 13.2 years, mean duration of illness 20.6 ± 18.7 years, and mean time since the most recent episode of 1.74 ± 0.44 years (Table 1). Of the 96 patients, 19 (19.8%) were dropped from the study for all-cause discontinuation. The mean daily dose of risperidone LAI at the 6-month study endpoint was 37.7 ± 11.2 mg. During the 6-month study period, ten of the 96 patients (10.4%) relapsed, a rate slightly lower than the 12.2% relapse rate in a Phase III Japanese trial of risperidone LAI monotherapy.[10] From baseline to 6 months, there were significant improvements in BPRS total scores ($P = 0.0031$), BPRS positive subscale scores ($P = 0.0451$), BPRS negative subscale scores ($P < 0.0001$), BPRS general subscale scores ($P = 0.0031$), and GAF ($P < 0.0001$, Table 2).

Table 1 Demographics of participants at baseline

Enrolled patients, n	96
Gender (males/females), n	52/44
Age at recruitment, years, mean (SD)	45.4 (13.2)
Period since recent episode, years, mean (SD)	1.74 (0.440)
Duration of illness, days, mean (SD)	7515 (6826)
Brief Psychiatric Rating Scale score at recruitment, mean (SD)	39.0 (13.2)
Clinical Global Impression-Severity, mean (SD) Concomitant drugs	3.86 (0.985)
Antipsychotic, n (%) [mean dose (SD)][a]	59 (61.5) [507 (631)]
Anxiolytics/hypnotics, n (%) [mean dose (SD)][b]	43 (59.7) [9.89 (20.3)]
Mood stabilizers, n (%)	7 (9.72)
Antiparkinsonian drugs, n (%)	15 (20.8)

Notes: [a]Chlorpromazine equivalent; [b]diazepam equivalent.
Abbreviation: SD, standard deviation.

Discussion

The present study is the first clinical trial examining the effectiveness of add-on COMPASS in preventing relapse in Japanese patients with schizophrenia treated with risperidone LAI. The relapse rate we observed, ie, 10.4%, was slightly lower than the 12.2% rate observed in a previous Phase III trial of risperidone LAI monotherapy in Japan.[10] "Returning to daily life" should be regarded as the highest priority treatment goal for patients with schizophrenia. This does not only mean returning to their previous community but recovering a sound relationship with society as a whole in a form suitable to realize their dreams and hopes.

COMPASS likely benefited patients and helped prevent relapse for several reasons. First, patients learned that risperidone LAI was a form of treatment designed to prevent recurrence,[11,12] with stabilized blood concentrations. COMPASS emphasized that patient self-awareness of their physical and mental condition could reduce the relapse rate, and taught methods of coping with stress that can induce relapse and worsening of symptoms.[13] COMPASS was especially useful in teaching patients about social resources and about concrete steps, and enabled them to talk about their dreams and hopes in their own words. Optimizing treatment in schizophrenia must take into account the different stages of the illness, with target outcomes appropriate for each of these stages.[14] Both pharmacologic and psychoeducational interventions must be appropriate to the stage of the disease.[15,16]

This study had several limitations. First, only subjects who were being treated with a combination of the original psychoeducational program and risperidone LAI were evaluated. There was no control group, such as subjects being treated with risperidone LAI alone, or subjects being treated

Table 2 Results for efficacy and extrapyramidal symptoms

	Baseline (n = 96)	3 months (n = 92)		6 months (n = 92)	
	Mean scores (SE)	Mean change scores (SE)	P-value	Mean change scores (SE)	P-value[a]
Brief Psychiatric Rating Scale					
Total scores	39.0 (1.35)	−1.15 (1.09)	0.294	−3.82 (1.25)	0.0031*
Positive subscores	11.8 (0.558)	−0.286 (0.449)	0.526	−1.18 (0.584)	0.0451*
Negative subscores	5.90 (0.228)	−0.396 (0.164)	0.0178*	−0.804 (0.175)	<0.0001*
General subscores	21.4 (0.765)	−0.560 (0.620)	0.368	−2.07 (0.678)	0.0031*
Global assessment of functioning	47.4 (1.42)	4.95 (1.07)	<0.0001*	6.73 (1.20)	<0.0001*
Drug-induced extrapyramidal symptoms scale	2.52 (0.368)	−0.528 (0.238)	0.0293*	−0.571 (0.256)	0.0280*

Note: *Statistically significant.
Abbreviation: SE, standard error.

with oral antipsychotics plus conventional psychoeducation. Second, psychoeducation at baseline had effects on patients receiving risperidone LAI monotherapy. Psychoeducational programs were already implemented in some patients prior to initiation of risperidone LAI, with some patients expressing high treatment satisfaction at baseline. Thus, the true transitional efficacy of treatment with risperidone LAI and COMPASS must be explored in future prospective, randomized trials containing control groups. Finally, comedications were allowed during the study. Nevertheless, to our knowledge, this is the first completed study of COMPASS in patients with schizophrenia.

In conclusion, COMPASS may have a benefit in the treatment of schizophrenia. Owing to the small sample size and the lack of a comparator, double-blind, randomized controlled clinical trials are needed to explore further the utility of COMPASS in patients with schizophrenia.[17]

Acknowledgments

Disclosure

References

1. Conley RR, Kelly DL. Management of treatment resistance in schizophrenia. *Biol Psychiatry*. 2001;50:898–911.

2. Kishimoto T, Robenzadeh A, Leucht C, et al. Long-acting injectable vs oral antipsychotics for relapse prevention in schizophrenia: a meta-analysis of randomized trials. *Schizophr Bull*. January 2, 2013. [Epub ahead of print.]

3. Zhao Y, Iwata N. Multi-centered research of the effectiveness of combined therapies for people with schizophrenia – a Comprehensive Psycho-educational Approach and Scheme Set (COMPASS) while using risperidone long-acting injection therapy. Presented at the 3rd Biennial Schizophrenia International Research Conference, Florence, Italy, April 14–18, 2012.

4. Inagaki A, Inada T. Dose equivalence of psychotropic drugs. Part XXII: dose equivalence of depot antipsychotics III: risperidone long-acting injection. *Jpn J Clin Psychopharmacol*. 2010;13:1349–1353.

5. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. *Psychol Rep*. 1962;10:799–812.

6. Chaichan W. Olanzapine plus fluvoxamine and olanzapine alone for the treatment of an acute exacerbation of schizophrenia. *Psychiatry Clin Neurosci*. 2004;58:364–368.

7. Hall RC. Global assessment of functioning. A modified scale. *Psychosomatics*. 1995;36:267–275.

8. Inada T, Yagi G, Miura S. Extrapyramidal symptom profiles in Japanese patients with schizophrenia treated with olanzapine or haloperidol. *Schizophr Res*. 2002;57:227–238.

9. Birchwood M, Todd P, Jackson C. Early intervention in psychosis. The critical period hypothesis. *Br J Psychiatry Suppl*. 1998;172:53–59.

10. Kamijima K, Ishigooka J, YK. Comparison study between risperidone long-acting injectable and risperidone tablets in patients with schizophrenia. *Jpn J Clin Psychopharmacol*. 2009;12:1199–1222.

11. Robinson D, Woerner MG, Alvir JM, et al. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. *Arch Gen Psychiatry*. 1999;56:241–247.

12. Tiihonen J, Haukka J, Taylor M, Haddad PM, Patel MX, Korhonen P. A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. *Am J Psychiatry*. 2011;168: 603–609.

13. Aguglia E, Pascolo-Fabrici E, Bertossi F, Bassi M. Psychoeducational intervention and prevention of relapse among schizophrenic disorders in the Italian community psychiatric network. *Clin Pract Epidemiol Ment Health*. 2007;3:7.

14. Agius M, Goh C, Ulhaq S, McGorry P. The staging model in schizophrenia, and its clinical implications. *Psychiatr Danub*. 2010;22: 211–220.

15. Chan SW, Yip B, Tso S, Cheng BS, Tam W. Evaluation of a psychoeducation program for Chinese clients with schizophrenia and their family caregivers. *Patient Educ Couns*. 2009;75:67–76.

16. Pitschel-Walz G, Bauml J, Bender W, Engel RR, Wagner M, Kissling W. Psychoeducation and compliance in the treatment of schizophrenia: results of the Munich Psychosis Information Project Study. *J Clin Psychiatry*. 2006;67:443–452.

17. Chabannes JP, Bazin N, Leguay D, et al. Two-year study of relapse prevention by a new education program in schizophrenic patients treated with the same antipsychotic drug. *Eur Psychiatry*. 2008;23:8–13.