

RISPERIDONE LONG-ACTING INJECTABLE IN STABLE PATIENTS WITH SCHIZOPHRENIA OR RELATED DISORDERS SWITCHED FROM ORAL OLANZAPINE

F. Rosa¹, P. Thomas², A. Schreiner³, T. Sherif⁴

¹Instituto de Saúde de S. João de Deus - Casa de Saúde de S. Rafael, Angra do Heroísmo, Azores, Portugal; ²Université Lille, Neurosciences Fonctionnelles et Pathologies Hôpital M. Fontan, Lille, France;

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³Janssen-Cilag, Medical Affairs EMEA, Neuss, Germany; ⁴King Khalid National Guard Hospital, Jeddah, Saudi Arabia.

INTRODUCTION

Patients with schizophrenia or related disorders often experience residual symptoms or symptomatic relapse despite antipsychotic treatment. The most common reasons for switching antipsychotic therapy are lack of efficacy and side effects.¹ Switching between atypical antipsychotics is also common, with incomplete efficacy being the most common reason.² Switching among atypicals is largely justified by psychiatrists' perceptions of differences in efficacy. Excessive weight gain is the most common reason patients switch from olanzapine to another antipsychotic.³ Switching from olanzapine to risperidone may therefore offer some tolerability benefits.

Identifying and preventing inadequate adherence during maintenance treatment may also be important, since inadequate adherence significantly increases the risk for schizophrenia hospitalization.⁴ The use of long-acting injectable antipsychotic formulations can improve adherence.^{5,6,7}

Previous studies showed that successful switching between antipsychotics may be influenced by dosing strategies. In a randomized, open-label study of patients with schizophrenia or schizoaffective disorder switched from stable olanzapine doses to risperidone, risperidone discontinuation was least evident when patients used a gradual discontinuation of olanzapine over 2 weeks (12%) compared with a 50% olanzapine reduction at risperidone initiation followed by 1-week titration (28%), or abrupt olanzapine discontinuation (25%).⁸

The current study was designed to compare efficacy and safety after switching to risperidone long-acting injectable (RLAI) in nonacute patients with schizophrenia or schizoaffective disorder treated with stable doses of olanzapine and requiring a change in antipsychotic medication for insufficient treatment response (stable symptoms on high dosage of olanzapine), side effects, compliance issues, or patient request. Reasons for change were documented. Since tapering schedules have been shown to affect outcome,⁹ separate comparisons were performed for patients with 1- or 3-week tapering schedules.

METHODS

Study design

- 6-month, multicenter, prospective, open-label, randomized, single-arm trial
- Current study evaluated tolerability, safety, and efficacy of RLAI after switching from oral olanzapine

Subjects

- Symptomatically nonacute adults aged ≥ 18 years
- DSM-IV diagnosis of schizophrenia or schizoaffective disorder
- Treated with stable dose of olanzapine for ≥ 1 month before screening
- Documented reasons for change were:
 - Insufficient treatment response (stable symptoms on high level)
 - Side effects
 - Compliance
 - Subject request
- Exclusion criteria: known nonresponders to risperidone or reported previous risperidone hypersensitivity/intolerance; history of severe drug allergy/hypersensitivity; neuroleptic malignant syndrome; tardive dyskinesia

Treatment

- RLAI was initiated at a dose of 25 mg administered every 2 weeks:
 - Higher initiation doses were available for subjects suffering from persistent symptoms or those known to respond only to higher doses of antipsychotics
 - Dosages were adjusted as needed to 25, 37.5, or 50 mg every 2 weeks
- Risperidone-naïve patients received 2 mg oral risperidone daily for 2 days prior to RLAI initiation to ensure tolerability
- Subjects continued pre-study, stable olanzapine doses for the first 3 weeks of RLAI therapy to ensure antipsychotic coverage until RLAI reached therapeutic drug levels
- 3 weeks after initiating RLAI, oral olanzapine was tapered off over 1 or 3 weeks
- RLAI dose increases could be supplemented with 1–2 mg oral risperidone daily for the first 3 weeks after an RLAI increase. Oral risperidone supplementation was permitted in cases of worsening of psychotic symptoms between visits that required an immediate dose adjustment
- Concomitant therapy was permitted. Subjects using neuroleptics or other psychotropic medications prior to study enrollment were permitted to continue those medications at a stable dosage, provided they were being used to treat nonpsychotic conditions. Benzodiazepines were permitted for periods of ≤ 10 consecutive days

Outcome measures

- Baseline assessments:
 - Clinical Global Impression-Severity (CGI-S)
 - Laboratory tests (including random cholesterol and glucose)
 - Physical examination
- Positive and Negative Syndrome Scale (PANSS), CGI-S, and CGI-Change (CGI-C) were obtained at baseline and treatment weeks 4, 12, and 26 or endpoint
- In subjects with an increase in RLAI dosage, PANSS assessments were completed prior to injection with the next higher RLAI dosage
- Medical Outcome Survey Short Form (SF-36), Global Assessment of Functioning (GAF), and categorical patient treatment satisfaction rating from very poor to very good were recorded at baseline and weeks 12 and 26 or endpoint

Safety and tolerability

- Adverse events (AEs) and weight at screening, baseline, and treatment weeks 4, 12, and 26 or endpoint
- Extrapyramidal symptoms (EPS) at baseline and treatment weeks 4, 12, and 26 using the Extrapyramidal Symptom Rating Scale (ESRS)
- Physical examination, vital signs, and laboratory testing were performed at week 26 or endpoint.
- Waist and hip circumference was measured at baseline and week 26 or endpoint

Data analysis

- Demographics, disease characteristics, and efficacy and safety measures were assessed using descriptive statistics
- A subanalysis determining the differences between the 1- and 3-week taper schedules was conducted

RESULTS

Subjects

- 102 patients were screened and 98 enrolled to the study
- 96 evaluable subjects with at least one dose of RLAI (53 tapered within 1 week; 43 tapered over 3 weeks)
- Mean daily olanzapine dose at baseline was 24.2 ± 15.6 mg (19.2 ± 11.8 for 1-week taper patients and 29.9 ± 17.5 mg for 3-week taper patients)
- Mean number of days receiving olanzapine after the first dose of RLAI was 33.1 ± 42.1 days in patients tapered within 1 week and 44.7 ± 24.1 days in patients tapered within 3 weeks.
- Demographics were similar between groups (Table 1)
- Approximately 50% of patients had ≥ 1 concomitant illness, the most common being psychiatric (anxiety in 16%, insomnia in 4%, and depression in 2%) and cardiovascular (12.5%)
- Most patients were treated with 25 mg RLAI for the first 12 weeks and 37.5 mg at 26 weeks
- Mean RLAI dosage was 30.1 ± 6.3 mg during the first 12 weeks and 32.6 ± 7.1 mg during the first 26 weeks. Mean dose was not related to baseline severity
- Concomitant medications other than oral olanzapine were used by 4 patients at baseline and used or changed by 21 patients at 26 weeks of treatment. The most common concomitant therapies were benzodiazepines (57.3%), other permitted antipsychotics (20.8%), selective serotonin reuptake inhibitors (16.7%), and phenothiazines (13.5%)
- Treatment was completed by 79 (82.3%) patients, with similar completion rates between groups (83.0% for 1-week taper group and 81.4% for 3-week taper group). 12 of the 17 dropouts occurred after treatment week 12 (4 withdrew consent, 3 for AEs, 2 for injection refusal; 2 were lost to follow-up; and 6 for other reasons)
- Mean treatment duration was 162.7 ± 40.5 days

Efficacy

- Efficacy data were available for 96 patients with efficacy assessments performed at screening, baseline, and week 4
- Significant endpoint efficacy changes were observed for PANSS total scores, PANSS factors, CGI-S, and GAF ($P < 0.0001$) (Table 2)
 - Baseline to endpoint improvement in mean total PANSS was $\geq 20\%$ for 65.6% of patients, $\geq 30\%$ for 52.1%, $\geq 40\%$ for 41.7%, and $\geq 50\%$ for 31.3%
- Endpoint improvement in PANSS total and subscale scores and factors were significant for both groups ($P < 0.0001$)
 - Mean improvement in PANSS positive subscale was greater among patients tapered over 3 weeks (-6.3 within 3 weeks vs. -3.4 within 1 week)
 - Endpoint improvement in total PANSS scores for patients tapered within 1 week vs. 3 weeks was $\geq 20\%$ for 69.8% vs. 60.5%, $\geq 30\%$ for 50.9% vs. 53.5%, $\geq 40\%$ for 37.7% vs. 46.5%, and $\geq 50\%$ for 24.5% vs. 39.5%
- CGI-S scores represented moderate to severe illness in 65.3% of patients at baseline and 35.4% at endpoint (Figure 1A). CGI-C was improved in most patients, with 50% of patients much to very much improved (Figure 1B) with no between-group differences
- Endpoint changes in SF-36 scores were not significant for either group
- The percentage of patients reporting good to very good treatment satisfaction almost doubled from baseline to endpoint (Table 2)
- Relapse occurred in 7 patients, all tapered within 1 week. First identification of relapse occurred for 1 subject each at treatment weeks 12, 16, 18, and 21, and for 3 subjects at treatment week 27

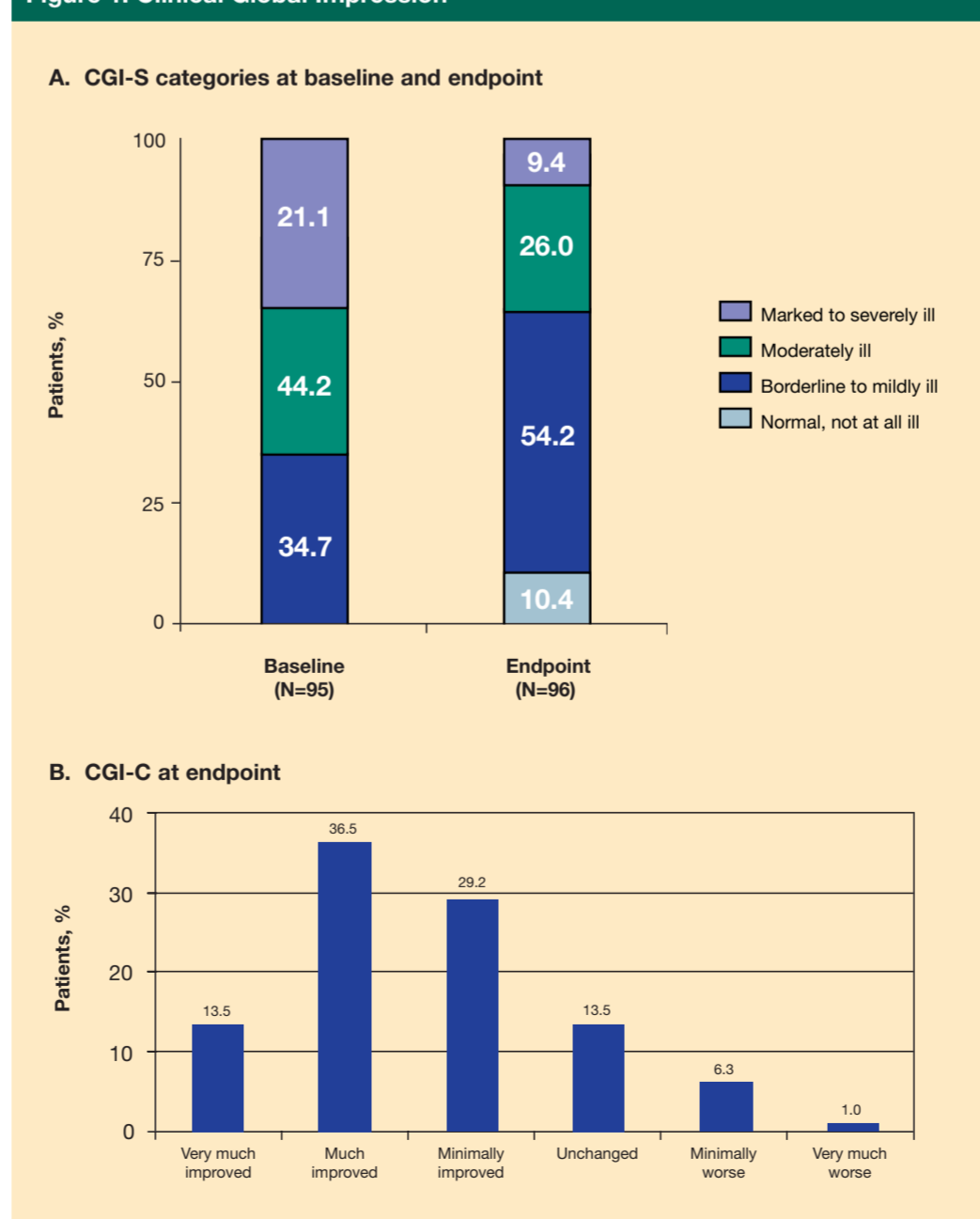
Safety and tolerability

- A total of 74 treatment-emergent AEs (TEAEs) were reported by 42 patients (42.9%).
- TEAEs occurring in $\geq 5\%$ of patients were agitation, insomnia, and schizophrenia, each reported by 5.1% of patients
- TEAEs were similar for both groups: 22 patients tapered within 1 week (40.0%) and 20 patients tapered within 3 weeks (46.5%)
- Most TEAEs were mild (34.5%) or moderate (49.0%) in severity. Causal relationship to study drug was considered to be possible, probable, or very likely for 30.6% of TEAEs. 83.3% of patients recovered from TEAEs

Table 1. Baseline demographics

Characteristic	Total sample N=96	1 week N=53	3 weeks N=43
Mean age, years (SD)	40.2 (14.0)	39.8 (12.8)	40.7 (15.4)
Gender, n (%)			
Male	74 (77.1)	39 (73.6)	35 (81.4)
Female	22 (22.9)	14 (26.4)	8 (18.6)
Race, n (%)			
Black	4 (4.2)	4 (7.5)	0
Caucasian	65 (67.7)	35 (66.0)	30 (69.8)
Hispanic	1 (1.0)	1 (1.9)	0
Oriental	3 (3.1)	3 (5.7)	0
Other	23 (24.0)	10 (18.9)	13 (30.2)
Mean baseline weight, kg (SD)	78.3 (17.1)	77.8 (18.1)	78.9 (15.7)
Mean baseline BMI, kg/m ² (SD)	26.9 (5.5)	26.5 (5.7)	27.3 (5.4)
Axis I diagnosis, n (%)			
Schizophrenia	73 (76.0)	42 (79.2)	31 (72.1)
Schizoaffective disorder	23 (24.0)	11 (20.8)	12 (27.9)
Mean age at onset of psychiatric symptoms, years (SD)	26.7 (8.2)	27.6 (8.8)	25.3 (7.1)
Mean number of psychiatric hospitalizations in the preceding 6 months, n (%)	1.1 (0.4)	1.1 (0.3)	1.1 (0.5)
Reason for changing antipsychotic, n (%)			
Insufficient negative symptom control	23 (24.0)	13 (24.5)	10 (23.3)
Insufficient positive symptom control	7 (7.3)	2 (3.8)	5 (11.6)
Insufficient general symptom control	17 (17.7)	4 (7.5)	13 (30.2)
Side effects – weight gain	15 (15.6)	11 (20.8)	4 (9.3)
Side effects – others	2 (2.1)	2 (3.8)	0
Patient request	13 (13.5)	9 (17.0)	4 (9.3)
Compliance issues	18 (18.8)	11 (20.8)	7 (16.3)
Other	1 (1.0)	1 (1.9)	0
Active concomitant disease, n (%)			
No	39 (40.6)	27 (50.9)	24 (55.8)
Yes	57 (59.4)	26 (49.1)	19 (44.2)

Figure 1. Clinical Global Impression

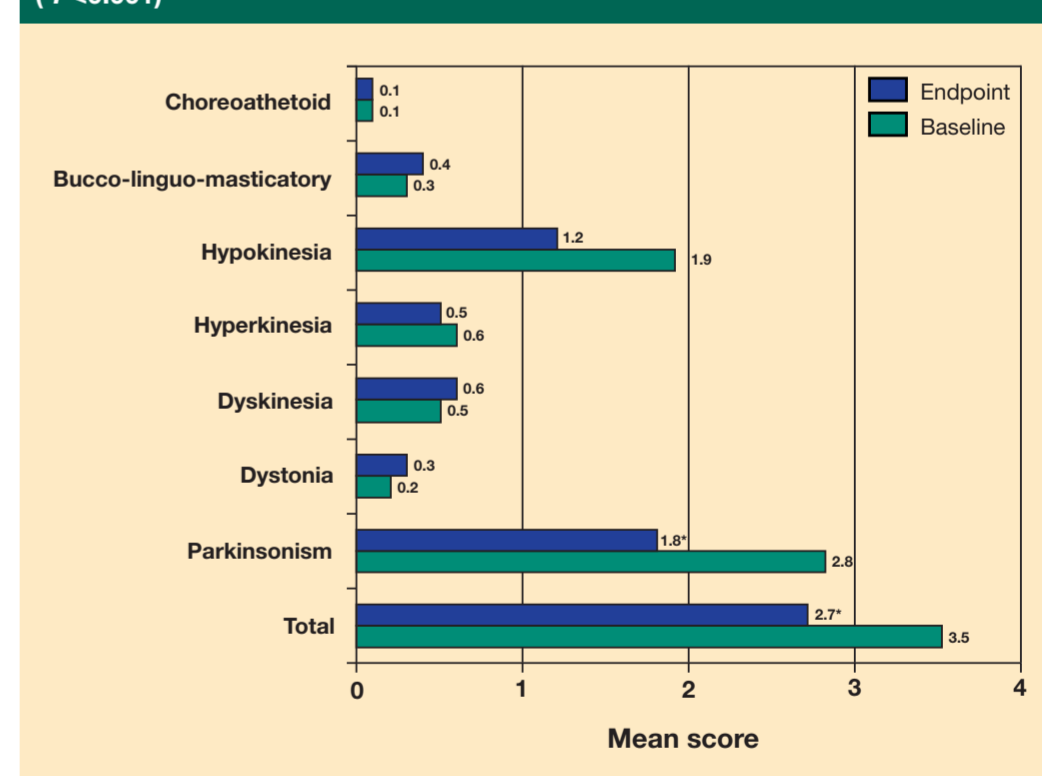


- 12 serious AEs were reported by 10 patients: 2 each for agitation and suicide attempt and 1 each for accidental exposure, drug detoxification, enuresis, extrapyramidal disorder, hostility, neuroleptic malignant syndrome, respiratory infection, and schizophrenia
- EPS were reported in 2 patients, both in the 3-week taper group (week 2 and 13)
- Significant improvements from baseline to endpoint were observed for total ESRS score ($P = 0.0005$), parkinsonism ($P = 0.0002$), and hypokinesia ($P = 0.0004$) (Figure 2)
- Mean change in total ESRS from baseline to endpoint was -0.6 (SD 3.1) for patients tapered within 1 week and -1.2 (SD 5.4) for patients tapered within 3 weeks. ESRS new-onset tardive dyskinesia was reported for 2 patients at visit 4 (week 26)
- Changes in vital signs were small and not clinically significant
- Changes in glucose and lipid levels were small. Elevation in fasting glucose and triglycerides levels at baseline had resolved at endpoint
- Mean change in weight from baseline to endpoint was 1.5 ± 12.3 kg for the entire sample, 0 ± 5.6 kg for patients tapered within 1 week, and 3.2 ± 17.2 kg for patients tapered within 3 weeks.
- Mean waist-to-hip ratio was unchanged from baseline to endpoint
- Reproductive/breast disorder AEs were reported for 2 patients (amenorrhea [n=1] and erectile dysfunction [n=1])

Table 2. Endpoint vs. baseline changes in secondary efficacy and functional measures

Measure	N=96		
	Baseline	Endpoint	Mean change (95% CI)
Mean PANSS, (SD)			
Total	84.1 (23.1)	64.5 (22.3)	-19.6 (-23.9 to -15.3)
General psychopathology subscale	41.9 (12.5)	32.3 (11.3)	-9.6 (-11.9 to -7.3)
Positive subscale	17.7 (6.9)	13.0 (5.0)	-4.7 (-6.0 to -3.4)
Negative subscale	24.5 (9.2)	19.1 (8.9)	-5.3 (-6.7 to -3.9)
Mean PANSS factor scores, (SD)			
Negative	23.2 (9.0)	17.8 (8.3)	-5.7 (-7.1 to -4.3)
Positive	22.4 (7.8)	16.8 (6.6)	-5.9 (-7.5 to -4.4)
Disorganized thoughts	19.8 (6.2)	15.5 (5.9)	-4.7 (-6.0 to -3.5)
Hostility/excitement	8.8 (4.6)	6.7 (3.0)	-2.4 (-3.2 to -1.5)
Anxiety/depression	9.9 (3.7)	7.5 (3.2)	-2.5 (-3.2 to -1.7)
Mean GAF, (SD)	55.0 (16.8)	64.2 (17.4)	9.2 (6.6 to 11.8)
Mean SF-36, (SD)			
Physical component	46.6 (8.9)	46.6 (10.3)	1.2 (-1.1 to 3.4)
Mental component	40.2 (11.9)	42.6 (11.9)	2.1 (-0.8 to 4.9)
Mean CGI-S, (SD)	3.8 (1.0)	3.1 (1.2)	-0.7 (-1.0 to -0.5)
CGI-S, n (%)			Not applicable
Not mentally ill	1 (1.0)	10 (10.4)	
Borderline mentally ill	17 (17.7)	20 (20.8)	
Mildly ill	21 (21.9)	32 (33.3)	
Moderately ill	44 (45.8)	25 (26.0)	
Markedly ill	10 (10.4)	6 (6.3)	
Severely ill	3 (3.1)	3 (3.1)	
Patient satisfaction, n (%)			Not applicable
Very good	7 (7.3)	23 (24.0)	
Good	23 (24.0)	35 (36.5)	
Moderate	44 (45.8)	24 (25.0)	
Poor	18 (18.8)	10 (10.4)	
Very poor	3 (3.1)	1 (1.0)	
No remark	1 (1.0)	3 (3.1)	

Figure 2. Mean ESRS total and subscale scores at baseline and endpoint (* $P < 0.001$)



CONCLUSIONS

- Switching from oral olanzapine to RLAI improved symptom control, global functioning, and patient satisfaction
- Symptomatic improvement occurred in both 1- and 3-week taper groups, with more pronounced improvement in PANSS total scores in the 3-week group
- RLAI was well tolerated
 - TEAEs were usually mild and transient
 - Significant improvements from baseline occurred for extrapyramidal symptoms, as measured by the ESRS
 - Modest weight gain occurred after switching from olanzapine to RLAI, but there was no significant change in hip-to-waist ratio
 - No difference in tolerability between 1- and 3-week taper groups

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