Postprint of a Study on the Efficacy and Safety of Injectable Risperidone Microspheres (II) in Maintenance Treatment for Patients with Schizophrenia

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Date: 2024-07-02T00:00:00+00:00

Abstract

Background Long-acting injectable antipsychotics represent an important option for maintenance treatment in patients with schizophrenia, effectively preventing relapse. Risperidone microspheres (II) for injection features an improved formulation that maintains stable plasma concentrations; however, relevant studies on clinical efficacy during the maintenance phase are currently lacking. Objective To evaluate the efficacy and safety of risperidone microspheres (II) for injection in patients with schizophrenia during the maintenance phase. Methods This study was a single-arm, self-controlled multicenter study. The study enrolled patients with maintenance-phase schizophrenia, aged 18-65 years, from three centers (Shanghai Mental Health Center, Hangzhou Seventh People's Hospital, and Suzhou Guangji Hospital) between May 2021 and May 2022. Subjects were switched from oral risperidone preparations to maintenance treatment with risperidone microspheres (II) for injection, administered every 2 weeks at doses of 25 mg, 37.5 mg, or 50 mg, with a 12-week follow-up period. The Personal and Social Performance Scale (PSP) was used to assess patients' social functioning at baseline and at the ends of weeks 2, 4, 8, and 12; the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression (CGI) scales were used to evaluate clinical symptoms and overall changes in illness severity; the European Quality of Life-5 Dimensions (EQ-5D) scale was used to assess patients' health status; the Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS), and Abnormal Involuntary Movement Scale (AIMS) were used to evaluate extrapyramidal symptoms, and laboratory parameters were collected. Results A total of 71 patients were enrolled. The total PSP scores at the ends of weeks 2, 4, 8, and 12 were

(48.20$\pm$24.65), (49.07$\pm$25.81), (50.46$\pm$26.96), *and*(51.85$\pm$28.16)*points*, *respectively*, *allhigherthanbaseline*[(43 points] (P<0.05). At week 12, the total PANSS score and scores on the positive symptom, negative symptom, and general psychopathology subscales were all reduced compared with baseline (P<0.05). The CGI-S score decreased from baseline (P<0.05), the CGI-I score at week 12 decreased compared with week 4 (P<0.01), and the EQ-5D score improved from baseline (P<0.05). Common adverse reactions included hyperprolactinemia, extrapyramidal symptoms (EPS), and dizziness. No serious adverse reactions or dropouts due to adverse reactions were observed. Conclusion Risperidone microspheres (II) for injection can effectively improve clinical symptoms in patients with schizophrenia during the maintenance phase and demonstrates good tolerability.

Full Text

Efficacy and Safety of Long-acting Risperidone Microspheres in the Maintenance Treatment of Schizophrenia

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Abstract

Background: Long-acting antipsychotics are an important option for maintenance treatment in patients with schizophrenia, effectively preventing relapse. Risperidone microspheres for injection (II) represent an improved formulation that maintains stable plasma drug concentrations, but there is currently a lack of research on its clinical efficacy during the maintenance phase. **Objective:** To evaluate the efficacy and safety of risperidone microspheres for injection (II) in maintenance-phase patients with schizophrenia. **Methods:** This was a single-arm, self-controlled, multicenter study. From May 2021 to May 2022, maintenance-phase schizophrenia patients aged 18-65 years were enrolled from three centers: Shanghai Mental Health Center, Hangzhou Seventh People's Hospital, and Suzhou Guangji Hospital. Patients were switched from oral risperidone to risperidone microspheres for injection (II) for maintenance treatment, receiving injections of 25 mg, 37.5 mg, or 50 mg every two weeks during the treatment period, with 12 weeks of follow-up. At baseline and at the ends of weeks 2, 4, 8, and 12, social functioning was

assessed using the Personal and Social Performance Scale (PSP); clinical symptoms and overall illness changes were evaluated using the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression Scale (CGI); health status was assessed using the European Quality of Life Five-Dimensional Questionnaire (EQ-5D); extrapyramidal symptoms (EPS) were evaluated using the Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS), and Abnormal Involuntary Movement Scale (AIMS); and laboratory indicators were collected. **Results:** A total of 71 patients were included. The total PSP scores at the ends of weeks 2, 4, 8, and 12 were $(48.20\$\pm24.65), (49.07\pm25.81), (50.46\pm26.96), and (51.85\pm28.16) points, respectively, all higher than baseline[(4$ points] (P<0.05). At week 12, PANSS total score, positive symptom scale, negative symptom scale, and general psychopathology scale scores were all reduced compared with baseline (P<0.05). CGI-S scores decreased compared with baseline (P<0.05), CGI-I scores at week 12 were lower than at week 4 (P<0.01), and EQ-5D scores improved compared with baseline (P<0.05). Common adverse reactions included elevated prolactin, extrapyramidal symptoms (EPS), and dizziness, with no serious adverse reactions or dropouts due to adverse reactions. **Conclusion:** Risperidone microspheres for injection (II) can effectively improve clinical symptoms in maintenance-phase patients with schizophrenia and is well tolerated.

Key words: Schizophrenia; Risperidone microspheres for injection (II); Maintenance treatment; Treatment outcome; Patient safety

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Schizophrenia is a severe chronic psychiatric illness with high disability and a high risk of relapse. High relapse rates can cause frustration for patients and their families, accompanied by high risks of hospitalization, heavy care burdens, and high treatment costs, thereby threatening patients' self-care abilities and social functioning [1-4]. Schizophrenia relapse is also accompanied by the development of neurofunctional deficits and treatment resistance, and patients who previously responded well to medication may develop treatment resistance [2]. Poor treatment adherence is one of the main causes of relapse. Antipsychotic drugs are currently the primary treatment for schizophrenia. After controlling symptoms during the acute phase, preventing disease relapse becomes an important and long-term treatment goal [3-4]. Maintenance treatment with antipsychotic drugs is one of the important measures to prevent relapse and can significantly reduce relapse risk [5-7]. Poor medication adherence has created significant development space for long-acting injections (LAI). Studies have confirmed that LAI treatment can effectively prevent relapse caused by poor adherence [6]. Guidelines from the UK's National Institute for Health and Care Excellence (NICE) and the World Federation of Societies of Biological Psychiatry (WFSBP) both recommend second-generation antipsychotic LAIs for maintenance treatment in schizophrenia patients [3,8]. The 2020 Expert Consensus on Long-acting Injectable Antipsychotics for Schizophrenia published by the Chinese Society of Psychiatry indicates that second-generation antipsychotic

LAIs can be used as a first-line treatment strategy for maintenance treatment in schizophrenia patients [7]. Multiple domestic and international studies have shown that using risperidone microspheres for injection can improve treatment effectiveness in patients with poor response, poor adherence, and significant adverse reactions, which is extremely important for improving treatment adherence, reducing adverse reactions, and improving social functioning [7,9-13].

Risperidone microspheres for injection (II) is the first formulation-improved second-generation antipsychotic LAI in China. Existing research has shown that it can rapidly take effect, effectively improve multidimensional symptoms in acute-phase schizophrenia patients, and has good tolerability [14]. Currently, clinical application research on risperidone microspheres for injection (II) in maintenance treatment of schizophrenia patients is limited. This study uses a single-arm, self-controlled, multicenter clinical research design to evaluate the efficacy and safety of risperidone microspheres for injection (II) in maintenance-phase schizophrenia patients.

1.1 Study Subjects

This study enrolled maintenance-phase schizophrenia patients from Shanghai Mental Health Center, Hangzhou Seventh People's Hospital, and Suzhou Guangji Hospital, with Shanghai Mental Health Center as the lead site. The study period was from May 2021 to May 2022. Inclusion criteria were: (1) meeting the diagnostic criteria for schizophrenia in the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10); (2) aged 18-65 years, regardless of gender; (3) meeting the criteria for maintenance-phase patients: stable condition, with total score $\leq$ 80 on the Positive and Negative Syndrome Scale (PANSS) [15] during screening and baseline; (4) currently receiving risperidone monotherapy or combined with other oral antipsychotics (except clozapine) with stable dosage for the past 3 months; (5) women of childbearing age with negative urine pregnancy test at screening; (6) patients and/or their guardians signed informed consent. Exclusion criteria were: (1) other severe mental disorders meeting ICD-10 diagnostic criteria; (2) history suggesting or investigator judgment of significant suicidal or violent tendencies currently or within the past 6 months, or those considered by clinical assessment to be at risk of suicidal or violent behavior; (3) high sensitivity to extrapyramidal adverse reactions of antipsychotic drugs, especially risperidone or paliperidone; (4) history of epilepsy or seizures; (5) receiving electroconvulsive therapy within 1 month before screening; (6) use of cytochrome P450 2D6 and 3A4 inhibitors or inducers within 2 weeks or 5 half-lives before screening (whichever is longer); (7) substance abuse within 6 months before screening; (8) presence of severe physical illness at screening. This study was approved by the Medical Ethics Committee of Shanghai Mental Health Center (ethics approval number: 2021-23).

1.2 Treatment Methods

Patients who met the inclusion criteria after screening were treated with risperidone microspheres for injection (II) (Rui Ke Tuo®, formerly known as Rui Xin Tuo®, Shandong Luye Pharmaceutical Co., Ltd.). Investigators converted to the long-acting injection based on the patient's daily dose of oral risperidone before enrollment. In this study, it was defined that if the patient's original oral risperidone dose did not exceed 4 mg/d, 25 mg was used as the starting injection dose; if the patient's original oral risperidone preparation was 5-6 mg/d, then 37.5 mg was used as the starting injection dose. Injections could be administered alternately in the gluteal muscles of both sides and the upper arms of both sides. Thereafter, injections were given once every 2 weeks, with a maximum dose not exceeding 50 mg/2 weeks, for a total treatment period of 12 weeks. After injecting Rui Ke Tuo®, the original oral risperidone preparation could be discontinued directly or gradually tapered to discontinuation. During the study, medications originally used to improve mood, sleep, extrapyramidal side effects, etc., could be continued, and any physical therapy was prohibited.

In this study, there were three methods for switching patients from oral risperidone to risperidone microspheres for injection (II): direct discontinuation, gradual tapering, and continued use. Direct discontinuation meant that after using risperidone microspheres for injection (II), the original oral risperidone preparation was immediately stopped, with the patient's original oral risperidone preparation not exceeding 4 mg/d. Gradual tapering meant slowly discontinuing the original oral risperidone preparation, generally when the patient was on a higher dose (5-6 mg/d). The continued use method meant simultaneously taking oral risperidone preparation after using risperidone microspheres for injection (II), maintaining a lower dose of oral risperidone preparation based on changes in the patient's clinical symptoms after switching.

1.3 Outcome Measures

1.3.1 Primary efficacy indicator: The Personal and Social Performance Scale (PSP) [16] was used at baseline and at the ends of weeks 2, 4, 8, and 12 to assess patients' social functioning, including four aspects: self-care, social role, interpersonal and family relationships, and disturbing and aggressive behavior. The total score is 100 points, with 91-100 indicating normal functioning, 71-90 indicating mild functional impairment, 31-70 indicating varying degrees of functional disability, and 1-30 indicating extremely low functioning. The change in PSP scores from baseline to study endpoint was used as the primary efficacy indicator.

1.3.2 Secondary efficacy indicators: (1) The PANSS scale was used at baseline and at the ends of weeks 2, 4, 8, and 12 to assess patients' psychiatric symptoms. Changes in PANSS scores were used to evaluate treatment efficacy, with PANSS subscale scores calculated, including the positive symptom scale, negative symptom scale, and general psychopathology scale. Higher scores in-

dicate more severe psychiatric symptoms. (2) The Clinical Global Impression (CGI) scale [17] was used to assess overall illness changes, including the CGI-Severity of Illness (CGI-S) and CGI-Global Improvement (CGI-I) scores, both rated on a 0-7 scale, with higher CGI-S scores indicating more severe illness. CGI-I includes: not assessed, very much improved, much improved, minimally improved, no change, minimally worse, much worse, and very much worse. CGI-S was assessed at baseline and at the ends of weeks 4, 8, and 12, while CGI-I was assessed at the ends of weeks 4, 8, and 12. (3) The European Quality of Life Five-Dimensional Questionnaire (EQ-5D) [18] was used at baseline and at the ends of weeks 4, 8, and 12 to assess patients' health status, including five aspects: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, with 100 points representing the best condition and 0 points representing the worst condition. Changes in PANSS scores, CGI-S, CGI-I, and EQ-5D scores from baseline to study endpoint were used as secondary efficacy indicators.

1.3.3 Safety indicators: At baseline and at weeks 2, 4, 8, and 12 visits, the Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS), and Abnormal Involuntary Movement Scale (AIMS) [17] were used to assess extrapyramidal symptoms (EPS). The SAS primarily assesses gait, rigidity of arms, head, and legs, tremor, and salivation, with a total of 10 items, each scored 0-4 across 5 levels. The BARS assesses objective and subjective manifestations of akathisia. The AIMS assesses abnormal movements potentially related to medication. Serum prolactin, blood routine, blood glucose, blood lipids, liver and kidney function were tested, and electrocardiograms were completed at baseline and study endpoint; adverse events (AE) were recorded at each visit. All AEs were classified by severity (mild, moderate, severe) based on whether treatment was required or daily life was affected.

1.3.4 Other indicators: In the study, a 5-point Likert scale was used to assess patient medication satisfaction, ranging from dissatisfied, slightly satisfied, satisfied, very satisfied, to extremely satisfied, with satisfied and above considered as patient satisfaction with medication. Assessments were conducted at the ends of weeks 4, 8, and 12.

1.4 Statistical Analysis

1.4.1 Analysis datasets: The Full Analysis Set (FAS) refers to the combination of eligible cases and dropout cases. When primary efficacy indicators were missing, the last observation carried forward (LOCF) method was used according to intention-to-treat (ITT) principles. The Per Protocol Set (PPS) refers to cases that met inclusion criteria, did not meet exclusion criteria, and completed the treatment protocol—that is, cases that complied with the study protocol, had good adherence, and completed the required content in the case report forms. PPS analysis was used for primary efficacy indicators. The Safety Set (SS) included actual data from patients who received at least one treatment and had safety indicator records. The denominator for adverse reaction incidence rates was the number of cases in the SS.

1.4.2 Statistical analysis methods: SAS 9.4 software was used for data analysis. Measurement data with normal distribution were described as (mean ± standard deviation), while non-normally distributed measurement data were described as median (P25, P75). Repeated measures across multiple time points were compared using one-way repeated measures ANOVA, and comparisons between each follow-up time point after treatment and baseline were made using the Bonferroni method. P<0.05 was considered statistically significant.

2 Results

2.1 General Information

A total of 72 patients were screened, 71 were formally enrolled, and 55 completed the entire study, with a dropout rate of 22.5%. The main reasons for dropout were loss to follow-up (8 cases, 11.3%) and withdrawal of informed consent (5 cases, 7.0%). The study flowchart is shown in Figure 1 [Figure 1: see original paper]. The mean age of patients was (38.9$±$12.7) years; 32 were male (45.1%) and 39 were female (54.9%); all were Han Chinese; the mean disease course was 39.55 (1.45, 122.80) months.

2.2 Risperidone Switching Methods

The number of patients using the three methods—direct discontinuation, gradual tapering, and continued use—were 17 (28.3%), 38 (63.3%), and 5 (8.4%), respectively. The mean switching time in the gradual tapering group was (18.8$±$13.1) days.

2.3 Efficacy Results

2.3.1 Primary efficacy indicator: FAS results showed no statistically significant difference in PSP total scores between baseline [(43.89$±$22.32) points] and week 2 [(48.20$±$24.65) points], week 4 [(49.07$±$25.81) points], week 8 [(50.46$±$26.96) points], and week 12 [(51.85$±$28.16) points] (F=0.986, P=0.415). However, PSP total scores at the ends of weeks 2, 4, 8, and 12 were all higher than baseline, with statistically significant differences (P<0.05).

2.3.2 Secondary efficacy indicators: Comparisons of PANSS total scores, positive symptom scale, negative symptom scale, general psychopathology scale, CGI-S, CGI-I, and ED-5Q scores at different visits showed statistically significant differences (P<0.01). Among these, PANSS total scores, positive symptom scale scores, negative symptom scale scores, general psychopathology scale scores, and CGI-S scores at the ends of weeks 2, 4, 8, and 12 were all lower than baseline, with statistically significant differences (P<0.05); ED-5Q scores at week 12 were higher than baseline, with statistically significant differences (P<0.05). The PANSS total score at week 12 was 27.6% lower than baseline. See Table 1 . In the study, CGI-I scores at week 12 were lower than at week 4, with statistically significant differences (P<0.01).

2.4 Safety Indicators

AEs were analyzed according to the SS (total of 71 cases). During the study, 33 adverse events occurred, with an incidence rate of 46.5%; among them, 28 were mild and 5 were moderate. No serious adverse events (SAE) occurred in the study. No patients dropped out due to adverse events during the switching from oral risperidone to risperidone microspheres for injection (II). Among these, 28 adverse reactions occurred, with an incidence rate of 39.4%, mainly various nervous system disorders. The most common adverse reactions were elevated serum prolactin (8 cases, 11.3%), EPS (7 cases, 9.9%), and dizziness (12 cases, 2.8%). Scores on the SAS, BARS, and AIMS scales were low at different time points. See Table 2 .

2.5 Other Indicators

Additionally, the proportion of patients who felt satisfied at week 4 was 95.1%, and all patients felt satisfied with the treatment at the end of week 12.

3 Discussion

Maintenance treatment for schizophrenia is an effective means of preventing relapse [11,13], and maintenance therapy can significantly reduce disease recurrence and rehospitalization rates [11]. Compared with oral antipsychotics, long-acting injection formulations can effectively help patients improve medication adherence and continuity, potentially improving antipsychotic efficacy [19-20]. Risperidone microspheres for injection (II), as the first formulation-improved second-generation antipsychotic long-acting injection in China, offers advantages in maintaining stable plasma drug concentrations, reducing dosing frequency, sustaining drug release, and allowing flexible dosing adjustments [21]. This study used risperidone microspheres for injection (II) in maintenance-phase schizophrenia patients to observe efficacy and safety. The study found that patients could be successfully switched from oral risperidone to risperidone microspheres for injection (II). The common switching methods were direct discontinuation, gradual tapering, and continued use of oral risperidone, with the specific method determined by the original daily dose of oral risperidone. No adverse events occurred during the switching period, no patients relapsed or discontinued treatment due to switching, and treatment adherence was good after switching to the long-acting injection. Therefore, this study indicates that switching from oral risperidone to risperidone microspheres for injection (II) long-acting injection is clinically practical and worthy of recommendation to clinicians.

This study used changes in PSP scores before and after treatment to evaluate the primary efficacy of switching from oral risperidone to risperidone microspheres for injection (II). The results showed that at week 12, the mean change in PSP score from baseline was 7.96 points, an increase of 18.1%. This change exceeds the threshold for maintenance-phase patients (4-7 point increase) and

has certain clinical significance [22]. However, the study did not find significant differences in PSP scores across time points, possibly due to insufficient sample size leading to non-significant results. The study used PANSS scores as a secondary efficacy indicator. At week 12, the PANSS total score decreased by 27.6% from baseline, which is comparable to previous studies [23]. This study defined a 20% reduction in PANSS score as improvement, while a related study on risperidone long-acting injection for maintenance-phase schizophrenia defined a PANSS reduction rate $\geq$ 25% as effective, showing a 77.1% effective rate at day 92 of treatment [24]. Additionally, PANSS subscale scores and CGI-S scores have clinical significance in evaluating efficacy. Studies have shown that negative symptoms after long-acting risperidone treatment are significantly correlated with PSP [25-26], and this study found improvement in PANSS negative symptom scores after treatment. A real-world study exploring the impact of monotherapy on social and cognitive function in maintenance-phase schizophrenia patients indicated that some independent variables related to negative symptoms (including various psychiatric symptom subscales and factors such as age and education) were significantly correlated with PSP scores [27]. Other PANSS subscale scores and CGI-S scores decreased with treatment duration, indicating that risperidone microspheres for injection (II) significantly improved psychiatric symptoms. The study found that ED-5Q scores improved from baseline after 12 weeks of treatment, suggesting improved health status after switching to the long-acting injection. These results demonstrate that risperidone microspheres for injection (II) is effective in improving clinical symptoms during the maintenance phase.

In terms of safety evaluation, the adverse reactions observed in this study (incidence rate 39.4%) were mainly various nervous system symptoms, with the most common adverse reactions related to extrapyramidal symptoms (9.9%). However, most were mild to moderate in severity, with no dropouts due to adverse reactions, and all adverse reactions resolved. These results are consistent with previous studies on the original formulation of risperidone microspheres for injection [28]. The common adverse reactions of risperidone microspheres for injection (II) are similar to other risperidone preparations. In this study, 8 patients (11.3%) had elevated serum prolactin at week 12. The prolactin-elevating effect of risperidone microspheres (II) is related to its blockade of D2 receptors in the tuberoinfundibular pathway [29], but the mean prolactin level decreased by (86$\pm$978.47) mU/L from baseline, suggesting that switching to risperidone microspheres (II) may improve prolactin levels compared with oral medication. This study indicates that risperidone microspheres for injection (II) is well tolerated.

The main limitations of this study are the lack of a control group (common schizophrenia medications) and only before-and-after self-comparison of treatment efficacy. Second, the sample size was limited, and future studies should expand the clinical trial sample size based on preliminary research to verify efficacy and safety. Additionally, applying therapeutic drug monitoring (TDM) and managing the efficacy and dose adjustment of long-acting risperidone mi-

crospheres are future directions for improving treatment strategies [30].

In summary, this study explored the efficacy and safety of risperidone microspheres for injection (II) in maintenance treatment of schizophrenia patients. The study found that switching from oral risperidone to risperidone microspheres for injection (II) is clinically feasible for maintenance-phase schizophrenia patients, can improve treatment adherence, and is worthy of recommendation. After switching, it can continuously improve psychiatric symptoms in maintenance-phase schizophrenia patients with good safety and tolerability. This study can provide further evidence for clinical research and practice in maintenance treatment of schizophrenia patients.

Author Contributions

LIU Caiping proposed the main research objectives, was responsible for study conception and design, implementation, manuscript writing, statistical analysis, and figure/table preparation and presentation; ZHANG Yanhua, TANG Jianping, WANG Chengpeng, XUE Fengfeng, WANG Huijuan, LI Chuanwei, and ZHANG Guangya collected and organized data; LI Huafang was responsible for quality control and review of the article, overall responsibility for the article, and supervision.

Conflict of Interest: This article has no conflict of interest.

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Table 1 Scores of PANSS and CGI-S and EQ-5D at each visit (FAS, mean±SD, points)

Table 2 Scores of SAS, BARS, and AIMS at each visit (SS, mean±SD, points)

Figure 1 Flowchart of participants

Note: Figure translations are in progress. See original paper for figures.