PSYCHOPATHOLOGY

Improved symptom control, functioning and satisfaction in French patients treated with long-acting injectable risperidone

La rispéridone injectable à action prolongée améliore le contrôle des symptômes, le fonctionnement et la satisfaction dans une population de patients français

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Objective. — To investigate the efficacy and tolerability of direct initiation of long-acting injectable risperidone (LAIR) in adults with schizophrenia or other psychotic disorders requiring a change of treatment.

Methods. — Patients clinically stable for one month or more on their previous medication received 25 mg of LAIR (increased to 37.5 or 50 mg, if necessary) every 14 days for six months.

Results. — Of 202 patients (70% male, mean age 38 years), the majority (86%) had DSM-IV schizophrenia (mainly paranoid). Previous treatments were atypical antipsychotics (65%), depot (34%) and oral (9%) conventional neuroleptics. Mean total positive and negative syndrome scale (PANSS) score was significantly reduced from baseline to treatment endpoint (79.4 versus 68.3, \( P < 0.001 \)), as were all subscale and symptom factor scores. The clinical global impression-disease severity (CGI-S), general assessment of functioning (GAF), health-related quality of life

KEYWORDS
Long-acting risperidone; Functioning; Tolerability; Quality of life

Summary

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Introduction

There is growing recognition that the optimal management of patients with schizophrenia or other psychotic disorders needs to extend beyond symptom control to encompass relapse prevention and improvement in the patient’s overall functional capacity and quality of life [22,27]. Studies with the atypical antipsychotics have shown that they can provide considerable improvements in global psychopathology and in the control of positive, negative, affective and cognitive symptoms compared with the conventional neuroleptics [22]. There is also evidence that they are more effective for the prevention of relapse [13,14,29] and that their use is associated with improved quality of life and satisfaction with treatment [4,27]. In the meantime it has even been suggested that symptomatic remission is an achievable objective for a significant proportion of patients with schizophrenia [3].

Whilst socioeconomic factors have an important impact on the quality of life of patients with schizophrenia, poorly controlled symptoms also adversely affect this important aspect of the patient’s overall perception of health [6,27]. Importantly, good adherence to antipsychotic medication regimens can contribute to a good quality of life, if the patient’s symptoms are reduced and few adverse effects are experienced [36]. However, the majority of patients are only partially compliant with oral antipsychotic regimens [32] and this has not improved with the introduction of the atypical antipsychotics [7,15,19,26,31].

Depot preparations of the conventional neuroleptics have a well-established role in the management of patients with schizophrenia. In addition to ensuring delivery of medication, their pharmacokinetic profiles reduce the daily fluctuations in plasma drug concentrations that are seen with orally administered drugs and so, can help to maximise both the efficacy and tolerability of treatment [5,17]. Patients who are established on treatment with a depot neuroleptic have a high degree of acceptance and satisfaction with their medication [37]. Nevertheless, the conventional depot neuroleptics have several limitations, including less efficacy and poorer tolerability, particularly with respect to movement disorders [7], than the atypical antipsychotics. The development of risperidone long-acting injectable (RLAI) has combined the advantages of a long-acting antipsychotic formulation with the benefits of the atypical agents [11,17].
Clinical studies with RLAI have shown that it is effective for both the short-term [24], and long-term [18] treatment of patients with schizophrenia. Patients have been shown to have significant improvements in psychopathology [18,24,28,35,40] and in health-related quality of life [35,36] after being changed to treatment with RLAI, regardless of their previous antipsychotic therapy. The change of treatment also led to a significant reduction in the severity of movement disorders [18,24,28,35,40].

In most previous trials patients received an oral risperidone run-in before beginning treatment with RLAI. This study, however, investigated the antipsychotic efficacy and safety of a direct transition to RLAI, without an oral risperidone run-in, in patients with schizophrenia or other psychotic disorders who required a change of treatment. We present here the results of a subgroup analysis performed in all patients from French study centres that were included in an international trial.

Subjects and methods

Data were derived from a six-month, nonrandomized, single arm, open-label, European trial that evaluated the safety and tolerability of a direct transition to RLAI without an oral risperidone run-in. The trial was performed in accordance with the guidelines of the International Conference on Harmonisation for Good Clinical Practice, as contained in the Declaration of Helsinki. In addition, the study protocol was approved by the Independent Ethics Committee at each of the participating study centres.

Patients

Patients, aged 18 years or older, with schizophrenia or other psychotic disorders according to the Diagnostic and Statistical Manual, fourth edition (DSM-IV), [2] treated with any antipsychotic medication, could be included in the study if the treating physician considered them to require a change of medication for any reason (e.g. lack of efficacy, side effects or poor compliance with current therapy). All patients were required to have been symptomatically stable and on constant doses of one or more antipsychotic agents for at least one month before the screening visit. Patients could be either hospitalised or outpatients at the time of enrolment and throughout the study.

Patients receiving their first antipsychotic treatment, who had received clozapine during the previous three months, participated in an investigational drug trial in the previous 30 days or had previously been shown to be either intolerant or a non-responder to risperidone therapy were excluded from the study. Other exclusion criteria included the presence of a serious unstable medical condition, including clinically relevant laboratory abnormalities, a history or current symptoms of tardive dyskinesia and a history of neuroleptic malignant syndrome. Pregnant or breast-feeding female patients were also ineligible and all other female subjects of childbearing potential were required to use adequate contraception and to have a negative urine pregnancy test at the screening visit.

All patients or their legal representatives provided written informed consent before their enrolment in the study.

Treatment

RLAI (Risperdal Consta®) was injected into the gluteal muscle every two weeks. The recommended starting dose was 25 mg but patients with persistent symptoms or who were known to respond only to higher dosages of antipsychotics could receive initial doses of either 37.5 or 50 mg. Thereafter, the dosage could be adjusted according to the patient’s symptoms and response to treatment.

Patients were transitioned directly from their previous antipsychotic medication to RLAI without an oral risperidone run-in. It was recommended that the tolerability of oral risperidone should be investigated before initiating treatment with RLAI in patients who had no history of previous risperidone use. All patients continued with their previous antipsychotic regimen for 21 days after the first injection of RLAI, after which it was stopped or tapered off over three days [35]. Patients being treated with conventional depots were changed according to a defined scheme based on the interval of the injection.

Patients could receive other psychotropic agents that had been initiated prior to the trial for other reasons (e.g. sleep induction or sedation) but the dose was required to remain stable. Oral risperidone supplementation could be used to manage any exacerbation of psychotic symptoms between study visits that required an immediate dose adjustment and also for up to 21 days following an increase in the dose of RLAI if an immediate clinical effect was needed. Finally, benzodiazepines could be used as rescue medication for periods of no more than 10 consecutive days.

Assessments

Efficacy was assessed at baseline and after one, three and six months of treatment (or treatment endpoint) using the positive and negative syndrome scale [25,33] and the clinical global impression-disease severity (CGI-S) [20]. Functional status was evaluated at baseline and six months by the global assessment of functioning (GAF) scale, in which a score of 100 represents best possible functioning [2]. The patient-rated SF-36 quality of life questionnaire [34,41], completed at baseline, three and six months was used to assess health-related quality of life, while patient satisfaction with treatment was rated at baseline and six months using a 5-point scale: very good, good, moderate, poor or very poor. Severity of movement disorders was assessed at baseline and after one, three and six months using the extrapyramidal symptoms rating scale (ESRS) [10]. Adverse events, vital signs and body weight were recorded by the investigator at each study visit.

Data analysis

The intention-to-treat (ITT) data set included all patients who received at least one injection of RLAI and completed at least one post-baseline efficacy assessment. This population formed the basis for all safety analyses and also for efficacy analyses using a last-observation-carried-forward (LOCF) analysis with respect to endpoint visits. Changes from baseline to endpoint in PANSS scores, CGI, SF-36, GAF, patient satisfaction with treatment and ESRS scores were...
analysed using the Wilcoxon signed rank test at the 5% significance level.

Results

A total of 202 patients were enrolled at study centres in France. One patient received no trial medication and so was not included in the ITT analysis. Of the remaining 201 patients, 69% completed the six-month study. The most common reason for early discontinuation was withdrawal of consent (10% of patients enrolled in the study). Other reasons for early discontinuation were insufficient efficacy (6%), loss to follow-up (4%), adverse events (4%), noncompliance (3%), death (0.5%) and other reasons (3%).

Baseline demographic data and disease characteristics for all patients who entered the study are shown in Table 1. Of those patients with schizophrenia, 64% had the paranoid subtype.

At trial entry, the most common treatment was an atypical antipsychotic (65%) or a conventional depot neuroleptic (34%; Table 2). The majority of patients (83%) were on monotherapy. Among the 34 patients (17%) on polytherapy, 25 were changed to RLAI monotherapy, while RLAI replaced one agent in the regimens of the remaining nine patients. The most frequently cited reasons for changing treatment to RLAI were noncompliance with previous medication according to physician assessment (49%), insufficient efficacy (24%) and side effects (mainly movement disorders) with the previous regimen (22%).

The majority of patients (82%) were started on RLAI at the 25 mg dose, while 22 and 33% were receiving 37.5 and 50 mg, respectively. During the six-month treatment period, 20% of patients received oral risperidone supplementation at a mean modal dose of 3.5 ± 1.7 mg and for a mean duration of 34.2 ± 40.5 days.

Symptom control

At baseline, the mean PANSS score was 79.4 ± 22.4 (range 31–129) and this was significantly reduced at treatment endpoint (68.3 ± 26.3, range 30–145; P < 0.001). Improvement was apparent after one month of treatment and further reductions were seen with ongoing treatment during the six-month study period (Fig. 1). At endpoint, 40% of patients had a ≥20% improvement in the PANSS total score compared with baseline. In addition, significant improvements from baseline to endpoint (P < 0.001) were seen in the subscores for the PANSS positive (16.3 ± 6.5 versus 14.8 ± 7.7), negative (23.6 ± 7.9 versus 19.2 ± 7.9)

![Figure 1](image-url)
and general psychopathology subscales (39.5 ± 11.7 versus 34.2 ± 13.3) and also in the positive symptoms (20.9 ± 7.2 versus 18.3 ± 8.4), negative symptoms (22.1 ± 7.7 versus 17.8 ± 7.2), disorganized thoughts (18.8 ± 5.9 versus 16.1 ± 6.6) and anxiety/depression (9.9 ± 3.8 versus 8.5 ± 3.8) factors of Marder [33].

There was a significant improvement from baseline to endpoint in the CGI-S ($P < 0.001$). At baseline, no patients were considered to be 'normal, not ill', and this had increased to 9% at endpoint (Fig. 2).

**Functioning and quality of life**

There was an improvement in patients’ functioning over the duration of the study, with a significant increase in the mean GAF score from 54.3 ± 15.8 at baseline to 61.1 ± 19.5 at endpoint ($P < 0.001$).

There was an overall improvement in health-related quality of life during the six-month treatment period, with increases from baseline to endpoint ($P < 0.05$) reported in the mean scores for all factors of the SF-36 except bodily pain (Fig. 3). Clinically significant improvements (i.e. >5 points) [38] were seen for the role physical, general health, social functioning, role emotional and mental health factors.
monotherapy with either an atypical antipsychotic (n = 110; −2.7 points), or a conventional depot neuroleptic (n = 48; −7.2 points).

There were no clinically significant changes in vital signs during the six-month treatment period. Overall, the patients experienced small but nonsignificant increases from baseline to endpoint in mean body weight (76.1 ± 14.9 versus 76.6 ± 15.1 kg) and body mass index (26.0 ± 5.0 versus 26.2 ± 5.1 kg/m²).

Discussion

In this study, patients were transitioned directly from their previous antipsychotic therapy to treatment with RLAI without an oral risperidone run-in. They experienced significant improvement in symptom control, overall functioning and health-related quality of life. All these improvements were consistent with those reported in studies with RLAI that included an oral risperidone transition period [18,24,36] and also with other studies which have described a treatment change to RLAI without an oral run-in phase [30,35,39].

Patients entering the present study were required to be symptomatically stable and on a stable dose of their previous antipsychotic regimen in the month prior to enrolment. Thus, in the opinion of the investigator, there had been no appreciable change in psychotic symptoms during the previous month, regardless of the severity of those symptoms. It is striking, therefore, that antipsychotic efficacy was not simply maintained following the change of treatment to RLAI but that there were significant improvements in symptom control, as demonstrated by the reductions in PANSS scores and in the CGI-S, compared with the previous treatment. These improvements in symptom control were sustained throughout the study period and a downward trend in the PANSS total score was still apparent after six months of treatment with RLAI. Importantly, these improvements were apparent across all symptom types, as demonstrated by the significant reductions in the PANSS positive and negative subscales and symptom factors, in the general psychopathology subscale and in the anxiety/depression and disorganised thoughts factors. Furthermore, 9% of patients were considered to be 'normal, not ill' after six months of treatment with RLAI.

The reductions in the severity of psychotic symptoms were accompanied by improvements in the patients’ overall functional capacity, as demonstrated by the increased scores on the physician-assessed GAF and in the patient-reported SF-36 health-related quality of life questionnaire. These improvements were achieved without the need to treat the majority of patients with the highest available dose of RLAI; at treatment endpoint, only one-third of patients were receiving the 50 mg dose.

The change to treatment with RLAI was also associated with a beneficial effect on movement disorders, as evidenced by the significant reduction in ESRS scores after only one month of treatment and the sustained improvements that were seen with ongoing RLAI therapy. It is also notable that significant improvements in movement disorders were apparent even among those patients previously treated with an oral atypical antipsychotic.

The study had a high completion rate, while the dropout rate due to adverse events was low (4%). Overall, the tolerability profile in the present study was comparable with that reported previously for RLAI [11,16,18,24,35]. Only one patient reported sexual dysfunction as an adverse event. Nevertheless, the benefits of the current treatment with respect to potentially hormone-related adverse events may be due to the more stable plasma levels that are achieved with RLAI compared with oral risperidone [11,17]. In recent years, attention has been paid to a possible association between weight gain induced by some of the atypical antipsychotics and the risk of abnormal glucose metabolism and diabetes mellitus [1,9,12]. The small increase in body weight observed in the present study is similar to that reported previously for oral risperidone and RLAI [12]. In addition, the single case of new-onset diabetes mellitus in the present study (i.e. 0.5% incidence over six months) is in line with the annual incidence of 1% for type 2 diabetes among white Europeans aged 40–79 years [8].

In addition to the overall reduction in psychopathology, important findings of the present study were the improvements in functioning and patient satisfaction with treatment. Thus, the significant increase (6.8 points) in mean scores on the physician-assessed GAF indicated that an overall improvement in the patients’ functional capacity, towards levels enjoyed by the general population, was apparent in addition to the improvements in the symptoms of schizophrenia. The patients themselves reported significant improvements in their quality of life. Thus, statistically significant increases were seen in the mean scores for all components of the SF-36 questionnaire, except bodily pain and the improvements in the role physical, general health, social functioning, role emotional and mental health factors were considered to be clinically significant. These improvements in health-related quality of life were consistent with the findings of a previous placebo-controlled study of RLAI in patients with schizophrenia [36] and also of six-month and 12-month open-label trials [21,35]. Furthermore, the patients reported high levels of satisfaction with their treatment at the end of the six-month study period, with more than two-thirds rating it as ‘good’ or ‘very good’.

A number of different factors influence the health-related quality of life of patients with schizophrenia, including persistent psychopathology (particularly negative symptoms) [27] and the adverse effects of treatment, particularly movement disorders, sexual dysfunction and neuroleptic-induced dysphoria [4,27]. These factors can also adversely influence adherence with antipsychotic therapy. Thus, the overall reduction in symptom severity, including the significant decreases in scores on the PANS negative subscale and the negative symptoms factor, seen in the present study along with the significant improvements in movement disorders would help to explain the improvements in health-related quality of life and satisfaction with treatment. In turn, these improvements may have contributed to enhanced compliance with therapy. Only 3% of patients were withdrawn from the study early due to poor compliance with the RLAI regimen, whereas noncompliance with previous therapy was cited as a reason for changing treatment in almost half of the study population.

The role of long-acting antipsychotic formulations in facilitating compliance with medication and thereby helping
to prevent relapse and improve functional outcomes, is well-established [5,23]. The development of RLAI now makes it possible to provide this treatment with an atypical antipsychotic. The present study has shown that its use can improve symptom control, functioning and quality of life in patients who are considered to be clinically stable on other treatments, including conventional depot neuroleptics and oral atypical antipsychotics. RLAI is an important addition to the armamentarium of treatment options for patients requiring long-term antipsychotic therapy.

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