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Paliperidone palmitate versus oral antipsychotics in recently diagnosed schizophrenia

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ABSTRACT

Objective: Relapse and acute exacerbation are common in schizophrenia and may impact treatment response and outcome. Evidence is conflicting in respect to superiority of long-acting injectable antipsychotic therapies versus oral antipsychotics in relapse prevention. This randomized controlled study assessed the efficacy of paliperidone palmitate versus oral antipsychotics for relapse prevention.

Method: Eligible patients with a recent diagnosis of schizophrenia (within 1–5 years) were randomized 1:1 to paliperidone palmitate (n = 376) or oral antipsychotic monotherapy (n = 388) and entered a 2-week initial acute oral treatment phase. Patients who met predefined response criteria were eligible to enter the 24-month rater-blinded core treatment phase. Patients were evaluated for relapse, symptoms, functioning, quality of life, treatment satisfaction, and tolerability.

Results: In the core treatment phase, time to relapse was significantly longer in the paliperidone palmitate (n = 352) compared with the oral antipsychotics arm (n = 363): 85% of patients were relapse-free at 469 versus 249 days ($P = 0.019$). Significantly fewer patients receiving paliperidone palmitate met the relapse criteria (52 [14.8%] versus 76 [20.9%, oral antipsychotics]; $P = 0.032$), representing a 29.4% relative risk reduction. For paliperidone palmitate, a significantly greater improvement in Positive and Negative Syndrome Scale total score on Day 8 ($P = 0.021$) and a trend at endpoint ($P = 0.075$) were observed. Functioning improvements were comparable between treatment arms. No new safety signals were identified.

Conclusion: The observed time to relapse superiority of paliperidone palmitate over oral antipsychotics provides further evidence for the value of long-acting injectable antipsychotic therapies in the treatment of schizophrenia, including during the early stages of illness.

1. Introduction

Despite the availability of effective treatment for schizophrenia, relapse and acute exacerbations are common (Emsley et al., 2013a). Response to treatment after relapse is variable; some patients display emergent refractoriness following relapse even when the interval between onset of first relapse symptoms and initiation of treatment is brief (Emsley et al., 2013b).

Evidence regarding the superiority of long-acting injectable antipsychotic therapies (LATs) over oral antipsychotics in terms of relapse prevention is conflicting (Leucht et al., 2011; Kishimoto et al., 2013; Kishimoto et al., 2014), with long-term comparisons scarce (Kane et al., 2010; Rosenheck et al., 2011). Hence, naturalistic and

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appropriately designed studies are needed to compare these treatment options (Kirson et al., 2013; Alphs et al., 2014), particularly in recently diagnosed patients with schizophrenia. The Prevention of Relapse with Oral Antipsychotics versus Injectable Paliperidone Palmitate (PROSIPAL) study was a randomized controlled, open-label, rater-blinded study that assessed the efficacy of paliperidone palmitate (PP) (Janssen-Cilag International NV, 2015), an atypical LAT, compared with oral antipsychotic monotherapy, in recently diagnosed patients with schizophrenia.

2. Methods

2.1. Study design

This multicenter, randomized, prospective, active-controlled, open-label, rater-blinded, international 24-month study in recently diagnosed (within 1–5 years) patients with schizophrenia (NCT01081769) was conducted in 141 centers across 26 countries (Appendix); it comprised a 2-week initial acute oral treatment phase and a 24-month core treatment phase.

Patients expected by the investigator to benefit from switching to one of the study medications were eligible to enter the initial acute oral treatment phase; patients were eligible for the core treatment phase if they then met all predefined response criteria:

- A score of ≤4 for at least four of the following Positive and Negative Syndrome Scale (PANSS) items: P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), P6 (suspiciousness/persecution), P7 (hostility), and G8 (uncooperativeness) and
- Clinical Global Impression-Severity (CGI-S) score ≤ 4, and
- No intolerable side effects of study medication.

Patients were maintained on PP or on the same oral antipsychotic (aripiprazole, quetiapine, olanzapine, paliperidone extended-release [ER], risperidone, or haloperidol as clinically indicated by the investigator) until the end of the core treatment phase, or until relapse or withdrawal from study.

The protocol was reviewed and approved by the Independent Ethics Committee/Institutional Review Board in each participating country. The study was conducted in accordance with the Declaration of Helsinki (2008) and Good Clinical Practice (International Conference on Harmonisation). Eligible patients were informed of the risks and benefits of the trial and were required to provide written informed consent for participation during an initial screening visit (Visit 1 [Day −14]). Standard medical and psychiatric assessments were completed to confirm the patients' clinical history and current symptomatology.

2.2. Subjects

2.2.1. Key inclusion criteria

Patients experiencing an acute episode of schizophrenia with a PANSS total score of 70–120 at screening were eligible for this study if aged 18–65 years, with a diagnosis of schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders (Fourth edition) criteria made 1–5 years previously and a history of ≥2 relapses requiring psychiatric hospitalization in the preceding 24 months; this may have included the current acute episode.

2.2.2. Key exclusion criteria

Patients were not eligible if they were antipsychotic-naive, considered by the investigator to be treatment-resistant or unsuitable for treatment with an atypical oral antipsychotic or oral haloperidol monotherapy, or had received clozapine within the previous 3 months. Other exclusion criteria included use of LATs within three injection cycles before screening, starting a psychotherapy program within 2 months preceding baseline, a history or current symptoms of tardive dyskinesia or a history of neuroleptic malignant syndrome, or involuntary hospitalization.

2.3. Treatment

2.3.1. Initial 2-week acute oral treatment phase

After screening, patients were randomized (1:1) to either PP or oral antipsychotic treatment and immediately entered the 2-week initial acute oral treatment phase. Patients randomized to PP had their previous oral antipsychotic replaced with oral paliperidone ER (dose range: 3–12 mg once daily). Patients randomized to oral antipsychotics had their previous oral antipsychotic (Supplementary Table 1) replaced with an oral antipsychotic different to the one they were using when they relapsed, as clinically indicated by the investigator. In both treatment arms, previous oral antipsychotics were tapered off over a maximum of 7 days.

A maximum of five, from a possible six, different oral antipsychotics (haloperidol plus four out of five oral atypical antipsychotics) were available to each study site; investigators could choose to prescribe any to the first randomized patient at their site. Subsequent patients were each prescribed a different oral antipsychotic at the investigator's discretion, to ensure equal distribution of medications. If ≥4 patients were allocated to the oral antipsychotic arm at a single site, all treatments were again made available to that site such that for the fifth patient the investigator was again able to choose from five oral antipsychotics. Oral antipsychotics were dispensed for self-administration and at each visit; patients were reminded to take their medication. The investigator or designated study personnel maintained a log of all drugs dispensed and returned (pill counts) at each visit; no routine blood level tests were conducted. Drug supplies for each patient were inventoried and accounted for throughout the study.

2.3.2. 24-month core treatment phase

Patients randomized to PP received intramuscular PP 150 mg eq. on Day 1 (deltoid), 100 mg eq. on Day 8 (deltoid), 75 mg eq. on Day 38 (deltoid or gluteal), and once monthly thereafter with flexible dosing 25–150 mg eq. (deltoid or gluteal). Patients randomized to the oral antipsychotic arm continued on the same drug that they had been prescribed in the initial acute oral treatment phase, at the dose defined by the investigator. Dose adjustments were permissible throughout the study within the locally-approved dose range. Assessments were performed on Day 1, Day 8, and then monthly for the first 4 months, at 6 months and quarterly thereafter until Month 24. Adverse events and concomitant medications were recorded continuously. Upon relapse, treatment with study medication was terminated; an alternative antipsychotic could be started at the investigator's discretion.

2.4. Efficacy assessments

The primary efficacy outcome was time to relapse per criteria described by Csernansky et al. (2002) (Appendix). Secondary outcomes included the proportion of patients with relapse at endpoint, PANSS total and subscale scores, Marder factor scores (Marder et al., 1997), percentage of treatment responders (≥30% decrease in PANSS total score from baseline to last observation carried forward endpoint [LOCF, 24 months or at early discontinuation]), CGI-S and Clinical Global Impression-Change (CGI-C) (Guy, 1972), Personal and Social Performance (PSP) scale (Morosini et al., 2000), Short Form (36) Health Survey (SF-36) (Ware and Sherbourne, 1992, Ware and Gandek, 1994), European Quality of Life-5 Dimensions (EQ-5D) (EuroQol Group, 1990), Subjective Well-Being under Neuroleptics Scale (SWN-S) (Naber, 1995), patient treatment satisfaction (Treatment Satisfaction Questionnaire for Medication; TSQM) (Atkinson et al., 2004), and physician's treatment satisfaction (7-point categorical scale).