Schizophrenia Research 132 (2011) 28–34

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Effects of acute paliperidone palmitate treatment in subjects with schizophrenia recently treated with oral risperidone☆

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ARTICLE INFO

Article history:
Received 4 March 2011
Received in revised form 9 June 2011
Accepted 15 June 2011
Available online 20 July 2011

Keywords:
Atypical antipsychotic
Long-acting injectable
Paliperidone palmitate
Risperidone
Schizophrenia

ABSTRACT

Objective: To examine efficacy and safety of acute treatment with paliperidone palmitate in subjects with schizophrenia whose disease remained symptomatic despite recent treatment with oral risperidone.
Methods: Post hoc analysis of a 13-week, double-blind, placebo-controlled study of subjects with symptomatic schizophrenia randomized to paliperidone palmitate 39, 156, or 234 mg (25, 100, or 150 mg equivalents of paliperidone) or placebo. Paliperidone palmitate subjects received a 234-mg day 1 dose, followed by their assigned dose on day 8 and monthly thereafter. Subjects treated with oral risperidone within 2 weeks before randomization regardless of duration were included. Assessments: PANSS, CGI-S, PSP scores; AEs. ANCOVA models with LOCF methodology evaluated treatment group differences.
Results: 216 subjects received prior oral risperidone (paliperidone palmitate 39 mg, $n=53$; 156 mg, $n=58$; 234 mg, $n=48$; placebo, $n=57$). Median prior risperidone use was 22 days. Significant improvement was observed with paliperidone palmitate 156-mg or 234-mg versus placebo in least-squares mean (SE) score change at end point in PANSS total (156 mg, −15.8 [3.0], $p=0.0001$; 234 mg, −17.6 [3.2], $p=0.0001$), CGI-S (156 mg, −0.9 [0.2], $p=0.0068$; 234 mg, −1.1 [0.2], $p=0.0003$), and PSP (156 mg, 10.7 [2.3], $p=0.0061$; 234 mg, 12.9 [2.4], $p=0.0009$). Most common AEs (≥10%) in any paliperidone palmitate group were insomnia, anxiety, and headache.
Conclusions: In subjects with schizophrenia who recently received oral risperidone but who remained symptomatic, acute treatment with monthly doses of 156-mg and 234-mg paliperidone palmitate significantly improved clinical symptoms, global illness ratings, and functioning compared with placebo, with no unexpected safety findings.

1. Introduction

Poor treatment adherence increases the risk for relapse, rehospitalization, attempted suicide, and clinical and functional deterioration and remains a frequent problem among patients with schizophrenia who are prescribed oral medications (Weiden et al., 2004; Nasrallah, 2007; Lindenmayer et al., 2009; Novick et al., 2010). In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), 74% of subjects discontinued their assigned oral antipsychotic treatment for any reason before 18 months (Lieberman et al., 2005). These results demonstrate the significant unmet treatment needs with the existing treatment approaches for schizophrenia and suggest that maximizing treatment continuity may represent a key opportunity for improving patient outcomes.

Long-acting injectable antipsychotics may offer a solution to the need for better treatment continuity because they simplify the medication regimen (Nasrallah, 2007; Velligan et al., 2009; Buchanan et al., 2010). In addition, bioavailability for long-acting injectable drugs is not diminished because of gastrointestinal absorption or first-pass hepatic metabolism. These differences in bioavailability between oral and injected drugs may result in lower relative lower dose requirements and less variable exposure for injected compounds compared with oral agents to achieve similar outcomes (McEvoy, 2006; Kane and Carcia-Ribera, 2009). Also, the time to a subtherapeutic level after missing a dose also is lengthened considerably. Furthermore, use of a long-acting injectable agent can promote contact between patients and treatment teams and allows the clinical team to readily recognize missed doses and respond accordingly (Ereshefsky and Mascarenas, 2003; Nasrallah, 2007; Velligan et al., 2009).

Paliperidone palmitate, the palmitate ester of paliperidone (9-hydroxyrisperidone), is a once-monthly injectable atypical antipsychotic indicated for the acute and maintenance treatment of

☆ Previous Presentation: Presented at the 163rd Annual Meeting of the American Psychiatric Association, May 22-26, 2010, New Orleans, Louisiana, USA.

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doi:10.1016/j.schres.2011.06.016

schizophrenia (Citrome, 2010; Gopal et al., 2010a; Invega® Sustenna®, 2010a). The pharmacologically active entity (paliperidone) is metabolized via 4 primary pathways each metabolizing <10% of the total dose with the remaining 59% excreted unchanged in the urine (Vermeir et al., 2008). It undergoes only limited hepatic metabolism and is not extensively metabolized by the CYP2D6 pathway. Consequently, unlike risperidone, paliperidone does not require a dose adjustment in patients with mild to moderate hepatic impairment (Boom et al., 2009).

Paliperidone palmitate has been shown to be effective, and tolerated in patients with symptomatic schizophrenia (Gopal et al., 2010b; Hough et al., 2010; Kramer et al., 2010; Pandina et al., 2010). Paliperidone palmitate is hydrolyzed to paliperidone (9-hydroxyrisperidone), the primary active metabolite of risperidone (Invega® Sustenna®, 2010a); the pharmacologic activity of 9-hydroxyrisperidone is similar to that of risperidone (Risperdal®, 2010b). The pharmacologic relationship between risperidone and paliperidone palmitate raises questions about whether treatment with paliperidone palmitate is effective in patients who remain symptomatic despite recent treatment with risperidone. This post hoc analysis evaluated the efficacy and safety of acute treatment with paliperidone palmitate at doses of 39, 156, and 234 mg, without oral antipsychotic supplementation compared with placebo, for up to 13 weeks in subjects who have been recently treated with oral risperidone but still experiencing clinically significant symptoms.

2. Methods

This was a post hoc analysis of a randomized, double-blind, placebo-controlled, multicenter study of paliperidone palmitate in subjects with schizophrenia (Study ID: CRO12550). Methods and overall results have previously been reported in detail (Pandina et al., 2010).

2.1. Subjects

Subjects included in this analysis had an established diagnosis of schizophrenia per the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) (American Psychiatric Association, 2000) for at least 1 year before screening and had been treated with oral risperidone within 2 weeks of randomization regardless of duration. Prior risperidone use including dose and duration was determined by retrospective subject or clinician reports. Given the limitations of the data collected in the primary trial, it could not be determined if the duration and dose of prior treatment with risperidone had been optimized prior to switching to randomized medication. Participants were at least 18 years of age and had a Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) total score between 60 and 120 (inclusive) at baseline. Key exclusion criteria included a history of treatment resistance defined as failure to respond to 2 adequate studies of different antipsychotic medications (a minimum of 4 weeks at the subject's maximum tolerated dose) and significant risk of suicidal, homicidal, or violent ideation or behavior as clinically assessed by the investigator.

The original study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with Good Clinical Practices and applicable regulatory requirements. The original study protocol was reviewed by an independent ethics committee or an institutional review board at each study site, and all subjects provided written informed consent before entering the study.

2.2. Study medication

In this report, dosing of paliperidone palmitate is expressed as milligrams of paliperidone palmitate. However, paliperidone palmitate dosing also may be expressed as milligram equivalents (mg eq) of paliperidone, with 39, 78, 117, 156, and 234 mg of paliperidone palmitate being equivalent to 25, 50, 75, 100, and 150 mg eq of paliperidone, respectively (Citrome, 2010; Invega® Sustenna®, 2010a).

2.3. Study design, randomization, and blinding

There were two study periods: a screening period of up to 7 days for washout of disallowed psychotropic medications (including all antipsychotics other than those to which the subject was randomized) and a double-blind treatment period of 13 weeks. Subjects were randomly assigned (on a 1:1:1:1 basis) to fixed doses of acute treatment with paliperidone palmitate (39, 156, or 234 mg) or placebo. The placebo injection consisted of 20% Intralipid (200 mg/mL) injectable emulsion.

The initiation regimen consisted of injections on day 1 (234 mg paliperidone palmitate or matching placebo; deltoid muscle) and day 8 (paliperidone palmitate at 39, 156, or 234 mg, or placebo; deltoid or gluteal muscle), followed by similar once-monthly injections at days 36 and 64 (Invega® Sustenna®, 2010a). Subjects were required to continue their oral risperidone dosage regimen until the day before the initial injection of study medication. Subjects were required to be hospitalized from the day of the first injection on day 1 until the second injection on day 8.

2.4. Disallowed and concomitant medications

Use of all oral and injectable antipsychotics, (except the study medication) mood stabilizers, and anticonvulsants was prohibited during the treatment period. Permitted concomitant medications included antiparkinsonian medications or antihistamines for emerging or worsening extrapyramidal symptoms (EPS), antidepressants (except for nonselective or irreversible monoamine oxidase inhibitors) if at stable doses for at least 30 days before screening, zolpidem for the treatment of insomnia, and oral benzodiazepines as rescue medication for agitation, anxiety, or sleep difficulties.

2.5. Study assessments

Assessments were made at baseline and on days 4, 8, 22, 36, 64, and 92 (or end point). The primary efficacy endpoint was the change in the PANSS total score from baseline to the end of the double-blind treatment period (day 92 or last postbaseline assessment). Secondary efficacy endpoints included changes from baseline to end point on PANSS factor scores (Marder et al., 1997), the Clinical Global Impressions–Severity (CGI-S) score (Guy, 1976a), the Personal and Social Performance (PSP) scale (Morosini et al., 2000), and response (≥30% improvement in PANSS total score). Safety evaluations included the assessment of treatment-emergent adverse events (AEs), body weight, and laboratory values, including prolactin concentrations, lipid profiles, and fasting glucose levels. AEs were recorded using spontaneous reports and coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA version 10.1). Subjects were assessed for emergence of involuntary movement disorders using the Simpson-Angus Scale (SAS) (Simpson and Angus, 1970), the Barnes Akathisia Rating Scale (BARS) (Barnes, 1989), and the Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976b).

2.6. Analysis sets

All analyses were performed on the intent-to-treat (ITT) analysis set, which included all randomized subjects who received at least one dose of study medication and had both baseline assessment and at least one postbaseline efficacy assessment (PANSS, PSP, or CGI-S).