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Research paper

Rapid onset of treatment effects on psychosis, depression, and mania in patients with acute exacerbation of schizoaffective disorder following treatment with oral extended-release paliperidone

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ABSTRACT

Background: Patients with schizoaffective disorder (SCA) experience complicated interplays of psychotic, depressive, and manic symptoms. Paliperidone extended-release (pali ER) tablets have been shown to be efficacious in these patients, but treatment response has not been studied relative to the onset of effects for these symptom domains.

Methods: In a pooled analysis of data from two 6-week, randomized, placebo-controlled studies, the onset of treatment effects with oral pali ER was evaluated by symptom domain (psychosis, depression, mania) in patients with an acute SCA exacerbation. Subjects were categorized as having prominent psychotic (Positive and Negative Syndrome Scale score >70), depressive (Hamilton Rating Scale for Depression–21 score ≥ 16), or manic (Young Mania Rating Scale score ≥ 16) symptoms at baseline.

Results: Of the 614 patients in these analyses, 597 (97.2%), 411 (66.9%), and 488 (79.5%) had prominent psychotic, depressive, and manic symptoms at baseline, respectively. Pali ER treatment was associated with rapid and significant improvement of all three symptom domains versus placebo within 1 week of initiation, regardless of whether treatment was given as monotherapy or in combination with mood stabilizers and/or antidepressants. Adverse events were similar to those reported in the original published studies.

Limitations: This post hoc analysis of two phase 3 trials requires confirmation in prospective studies.

Conclusion: This pooled analysis suggests that treatment with pali ER is associated with rapid control of psychotic, depressive, and manic symptoms in patients with SCA. Its findings support the benefit of pali ER as a primary treatment for the management of SCA.

1. Introduction

The 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) reaffirms schizoaffective disorder (SCA) as a distinct diagnostic entity characterized by a mix of symptoms, including psychosis, depression, and mania, that are associated with schizophrenia and affective disorders (American Psychiatric Association [APA], 2013). SCA is about one-third as prevalent as schizophrenia (Canuso et al., 2010) and has a prognosis that is generally intermediate to that of schizophrenia and affective disorders (Canuso et al., 2010). SCA can be disabling and requires significant mental health resources (Kent et al., 1995), but treatment with antipsychotic medication can help manage symptoms and improve quality of life for patients with the disorder.

Historically, symptoms of SCA have been managed with symptom-specific concomitant medications that include antipsychotics, mood stabilizers, antidepressants, and anxiolytics (Olfson et al., 2009). More recently, large, well-controlled clinical trials of oral paliperidone extended-release (pali ER), administered as monotherapy or in combination with mood stabilizers and/or antidepressants, has helped establish the drug as a safe, effective, and acute treatment of SCA (Canuso et al., 2010b; Canuso et al., 2010a; Canuso et al., 2010c; Ortho-McNeil-Janssen Pharmaceuticals, Inc., 2011). In addition, a 15-month relapse-prevention study showed once-monthly paliperidone palmitate to be an effective long-term maintenance treatment for SCA when given as monotherapy or in combination with mood stabilizers or antidepressants (Fu et al., 2015).

Because patients with SCA experience various types and severities of psychotic, depressive, and/or manic symptoms, understanding the extent and timing of treatment effects on each of

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these symptom groups and providing insights into the use of concomitant therapies are important for clinical decision-making. This pooled analysis of two large registration trials in acutely exacerbated subjects with SCA evaluated the pattern and timing of onset of pali ER treatment effects for the three primary SCA symptom domains: psychosis, depression, and mania.

2. Methods

2.1. Study design

Pooled data from two 6-week, randomized, placebo-controlled studies of pali ER treatment versus placebo in patients with SCA ($N=614$) were examined in post hoc analyses (Canuso et al., 2010c). Full details of these studies have been reported elsewhere (Canuso et al., 2010b; Canuso et al., 2010a).

Briefly, in study 1 (ClinicalTrials.gov identifier: NCT00412373) (Canuso et al., 2010b), acutely exacerbated subjects with SCA were randomly assigned in a 2:1 ratio to receive 6 mg/day pali ER or placebo. After day 4, the dosage could be adjusted in 3-mg increments in a range of 3 to 12 mg/day. In study 2 (ClinicalTrials.gov identifier: NCT00397033) (Canuso et al., 2010a), acutely exacerbated subjects with SCA were randomly assigned in a 1:1:1 ratio to receive lower-dose pali ER (6 mg/day, with an option to reduce to 3 mg/day), higher-dose pali ER (12 mg/day, with an option to reduce to 9 mg/day), or placebo. Dose adjustments were permitted until day 15 for both studies, after which time no further changes were allowed. Subjects could receive concomitant treatment with mood stabilizers and/or antidepressants if they had been treated with a stable dose within 30 days of screening (Canuso et al., 2010b, 2010a). During screening, all other antipsychotic medications were discontinued in a washout period of 2 to 5 days. Subjects on stable doses of benzodiazepines at study entry could continue at the same dose throughout the study. New use of benzodiazepines was permitted for the first 15 days of the study.

The final protocols of the original studies were approved by participating independent ethics committees or institutional review boards (Canuso et al., 2010b, 2010a). The studies were conducted in accordance with the ethical principles of the Declaration of Helsinki, and each subject provided written informed consent according to local requirements after receiving a full explanation of the study.

2.2. Participants

Subjects in these studies were aged 18 to 65 years with a current diagnosis of SCA, as confirmed by the Structured Clinical Interview for DSM (DSM-IV) Disorders (American Psychiatric Association, 1994). All were experiencing an acute exacerbation of illness and prominent mood symptoms of <4 weeks in duration, as evidenced by the Young Mania Rating Scale (YMRS) (Young et al., 1978) total score of ≥ 16 and/or the Hamilton Rating Scale for Depression, 21-item version (HAM-D-21) (Hamilton, 1960) total score ≥ 16; the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) total score ≥ 60; and the PANSS score ≥ 4 on two or more items (ie, hostility, excitement, tension, uncooperativeness, or poor impulse control) (Canuso et al., 2010c).

For this analysis, subjects were categorized according to whether they displayed prominent psychotic (PANSS score >70), depressive (HAM-D-21 score ≥ 16), or manic (YMRS score ≥ 16) symptoms at baseline. Subjects could be included in more than one category because baseline symptom categories were not mutually exclusive. Specifically, a subject could present with prominent symptoms in more than one of these domains: psychotic, depressive, or manic.

2.3. Assessments

Efficacy of pali ER was assessed using the PANSS, the Clinical Global Impressions–Severity of Illness Scale for Schizoaffective Disorder (CGI-S-SCA), the HAM-D-21, and the YMRS. Assessments were performed at baseline, at day 4, and at weeks 1, 2, 3, 4, and 6 (Canuso et al., 2010b, 2010a).

Analysis end points were changes from baseline to day 4 and changes from baseline to weeks 1, 2, 3, 4, and 6 (end point) in PANSS, HAM-D-21, and YMRS total scores. Responder rates, defined as subjects with a $\geq 50\%$ decrease from baseline in symptom scale scores, were identified. The number of subjects who improved in all three domains (psychosis, depression, and mania) was measured at each time point and evaluated according to treatment type (ie, pali ER or placebo, administered as monotherapy or in combination with mood stabilizers and/or antidepressants). Clinically meaningful improvements in the PANSS, HAM-D-21, and YMRS were assessed and defined as a $\geq 30\%$ improvement (European Medicines Agency and Committee for Medicinal Products for Human Use (CHMP), 2012) or a ≥ 10-point decrease (Leucht et al., 2006) in the PANSS; a $\geq 50\%$ improvement (Furukawa et al., 2007) or ≥ 4-point decrease in the HAM-D-21 (Turkoz et al., 2013); and a $\geq 50\%$ improvement (Kemp et al., 2011) or ≥ 6-point decrease in the YMRS (Turkoz et al., 2013), respectively. Safety assessments for this analysis included adverse event (AE) reporting and were classified according to the Medical Dictionary for Regulatory Activities (MedDRA version 9.0).

2.4. Statistical analysis

The intention-to-treat (ITT) analysis set, defined as subjects who received at least one dose of study medication and had at least one postbaseline efficacy assessment, was used for efficacy and safety assessments. Between-group differences in continuous variables were evaluated using an analysis of covariance model with fixed effects for treatment, concomitant medication strata, study identification (ID), country nested within study ID, and baseline variable. Between-group differences in categorical variables were evaluated using a Cochran–Mantel–Haenszel test that controlled for concomitant medication strata, study ID, and country. Percentage differences were also examined using Fisher's exact test. Analyses of efficacy data involving changes from baseline to each assessment time point used the last-observation-carried-forward approach. No adjustments were made for multiplicity.

3. Results

3.1. Baseline Demographics and Clinical Characteristics

The majority of subjects had overlapping symptoms of psychosis, depression, and mania (Table 1). Of the 614 patients included in these analyses, 597 (97.2%), 411 (66.9%), and 488 (79.5%) had prominent psychotic, depressive, and manic symptoms, respectively. In the overall ITT analysis set, 414 and 200 subjects received pali ER and placebo, respectively. Baseline demographics and clinical characteristics are outlined in Table 1. Regardless of baseline symptoms, the mean age of subjects was 37 years, and approximately 50% were white. All subjects had acute psychotic symptoms at screening, and the majority (97.2%; 597/614) had prominent, continuous psychotic symptoms at the time they were randomly assigned to treatment. Approximately half (44.8%; 275/614) of the subjects were receiving concomitant mood stabilizers and/or antidepressants, with mood stabilizers used by 69.5% (191/275) and antidepressants by 49.1% (135/275) (Canuso et al., 2010c).