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Treatment of acute schizophrenia with paliperidone ER: Predictors for treatment response and benzodiazepine use

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ABSTRACT

The Paliperidone ER Treatment in Acute Intervention (PERTAIN) study was designed to explore treatment response, tolerability, and safety of flexible doses of paliperidone ER in patients with schizophrenia admitted for an acute exacerbation. This paper addresses a secondary analysis of PERTAIN data designed to explore predictors for treatment response, flexible dosing, and concomitant benzodiazepine use. This prospective, multicenter, phase 3b, open-label, single-arm, 6-week study used flexible doses of paliperidone ER (3 to 12 mg once daily) to treat patients hospitalized for an acute exacerbation of schizophrenia, reflecting more closely daily clinical practice. Predictive models were evaluated for paliperidone ER flexible dosing, treatment response, and concomitant treatment with benzodiazepines as distinct independent variables. For the analysis of explanatory variables, a stepwise logistic regression was used, taking into account patient age, gender, body mass index, diagnosis and duration of schizophrenia, number of prior hospitalizations, psychotic symptoms (PANSS), disease severity (CGI-S), and patient functioning (PSP) at baseline. Early response (defined as response within 2 weeks of treatment initiation) was also used as a predictor. Clinical response (defined as ≥30% decrease in PANSS total score and ≥1 point decrease in CGI-S from baseline to endpoint) was predicted by early clinical response ($p < 0.001$) and there was a trend for the diagnosis of paranoid schizophrenia vs. other types of schizophrenia to predict clinical response ($p = 0.0525$). High response (defined as ≥50% decrease in PANSS total score and ≥2 points decrease in CGI-S from baseline to endpoint) was predicted by early high response, higher baseline CGI-S, or female gender. More severely ill patients with a higher baseline CGI-S were twice likely to be treated concomitantly with a benzodiazepine.

1. Introduction

Demographic and baseline characteristics have been shown to predict treatment response in patients with schizophrenia or related disorders treated with typical or atypical antipsychotics (Emsley et al., 2006, 2007; Semiz et al., 2007). A good response to antipsychotic treatment has been predicted by older age, longer duration of symptoms before treatment, female gender, better treatment tolerability, and early symptom improvement (Agid et al., 2003; Nedopil et al., 1983). Family history, neurological abnormalities, and abnormalities in brain morphology and neurotransmitters have also been found to be associated with antipsychotic response (Awad, 1989; Bartkó et al., 1990). A recent cluster analysis categorized outcome for 2161 patients with schizophrenia or

Abbreviations: BMI, body mass index; CGI-S, Clinical Global Impression—Severity; CI, confidence interval; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; ER, extended release; OR, odds ratio; PANSS, Positive and Negative Syndrome Scale; PERTAIN, Paliperidone ER Treatment in Acute Intervention; PSP, Personal and Social Performance; SD, standard deviation.

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a related disorder who were treated with antipsychotic medications for 24–52 weeks in 6 double-blind, active control clinical trials in which one treatment arm used olanzapine (Lipkovich et al., 2009). One out of these six studies included only patients with first-episode schizophrenia and two others evaluated acutely psychotic patients. The other studies listed inclusion criteria for different levels of symptom severity based on standard severity measures, although acute, chronic, or first-episode patients were not specified. The cluster analysis identified several predictors for achieving a good outcome, including higher baseline quality of life and functioning, early reduction in positive symptoms (at 2 and 4 weeks), and lower akathisia scores. In contrast to the previous report by Nedopil et al. (1983), older age was associated with poor outcome in this cluster analysis. Data from two randomized, double-blind clinical trials treating schizophrenia with amisulpride or risperidone identified response predictors (Levine and Leucht, 2010). These studies were an 8-week study evaluating patients with acute exacerbations of schizophrenia and a 6-month study of patients with chronic schizophrenia with a recent worsening of symptoms. Pooled data from these trials were used to evaluate treatment response through 8 weeks of treatment, with response defined as a ≥50% reduction in Brief Psychiatric Rating Scale scores from baseline to week 8 in both trials and week 26 in the longer trial. Patient schizophrenia diagnoses were 62% paranoid, 24% disorganized, and 14% undifferentiated in the acute trial (Peuskens et al., 1999) and 73% paranoid, 12% disorganized, 9% undifferentiated, and 6% residual in the chronic study (Sechter et al., 2002). Aggregate analyses showed that responders were also likely to be diagnosed with a paranoid schizophrenia subtype (69%). While patients with moderately good response were more likely to be female, rapid responders were predominantly male. Poor responders tended to be older, have the greatest symptom severity scores at baseline, and have failed to achieve an early treatment response.

While more severe baseline symptom severity was associated with a poorer response to acute treatment of schizophrenia for both studies by Lipkovich et al. (2009) and Levine and Leucht (2010), this association has not been found in other studies (Crespo-Facorro et al., 2007; Tabatabaee et al., 2008). This apparent discrepancy may be at least partially explained by patients with lower baseline severity having difficulty achieving the high percentage of improvement required by some studies to be identified as responders (Crespo-Facorro et al., 2007).

Early treatment response has also been shown to be an important predictor of long-term efficacy. Treatment response at 2 or 4 weeks with atypical antipsychotics accurately predicts later treatment outcome (Change et al., 2006; Chen et al., 2009; Kinon et al., 2008; Leucht et al., 2008; Lin et al., 2007; Semiz et al., 2007). Furthermore, an analysis of data from 7 randomized, controlled antipsychotic trials treating 1708 patients with schizophrenia or schizophreniform disorder with amisulpride or another antipsychotic (haloperidol, flupenthixol, or risperidone) for 4–51 weeks showed that non-response after 1 week of treatment predicted non-response at 4 weeks with 90% specificity (Leucht et al., 2007).

Paliperidone ER (extended release) is approved for the treatment of schizophrenia and schizoaffective disorder, with efficacy and safety demonstrated in randomized controlled clinical trials (Canuso et al., 2010; Meltzer et al., 2008) and long-term open-label studies (Emsley et al., 2008). Significant improvement with paliperidone ER has been shown to occur early, during the first few days of treatment (Alphs et al., 2011; Davidson et al., 2007; Schmauss et al., 2012). The pragmatic flexible-dose Paliperidone ER Treatment in Acute Intervention (PERTAIN) study was designed to explore treatment response, tolerability, and safety of flexible doses of paliperidone ER (3–12 mg once daily) in patients with schizophrenia admitted for an acute exacerbation (Schmauss et al., 2012). Patients were recruited from acute clinical settings using less strict inclusion and exclusion criteria, for example, allowing patients with concomitant substance abuse and psychotropic comedications to participate. The primary efficacy and safety data from this study have been published, showing improvement in Positive and Negative Syndrome Scale (PANSS) total score ≥30% at 6-week endpoint in 66% and generally good tolerability (Schmauss et al., 2012). The following report describes a post-hoc secondary analysis of PERTAIN data designed to explore predictors for treatment response, dosing, and concomitant benzodiazepine use in patients with schizophrenia suffering from an acute episode and treated with flexible doses of paliperidone ER. Predictors identified in flexible-dosing regimens may add valuable information that is more applicable to representative clinical practices than predictors based on randomized fixed dosing regimens that may have resulted in suboptimal dosing since dose adjustments in individual patients were not permitted.

2. Methods

2.1. Study design

This prospective, multicenter, phase 3b, open-label, single-arm, 6-week study used flexible doses of paliperidone ER (3 to 12 mg once daily) to treat patients with an acute exacerbation of schizophrenia. The study was conducted in Europe and Israel from 4 July 2007 to 23 May 2008. The study was performed in accordance with the guidelines of the International Conference on Harmonization for Good Clinical Practice and the study protocol was approved by Independent Ethics Committees. Prior to study enrollment, all patients gave written informed consent. The analysis is based on a stepwise logistic regression seeking to identify statistically significant predictors of treatment outcome and dosing; primary efficacy and safety outcome data have been presented separately (Schmauss et al., 2012).

2.2. Patients

Adult patients aged ≥18 years with schizophrenia diagnosed using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria (DSM-IV) (American Psychiatric Association, APA, 1994) were enrolled if they experienced an acute exacerbation of schizophrenia with a baseline PANSS total score of ≥70 and if they agreed to ≥7 days of hospitalization. Female patients of child-bearing potential had to have a negative urine pregnancy test at screening and be using effective contraception. Pregnant and breastfeeding women were excluded. Key study exclusion criteria were: first antipsychotic treatment ever; treatment with clozapine or a long-acting injectable antipsychotic during the last 3 months; a history of significant medical illness, tardive dyskinesia, or neuroleptic malignant syndrome; or a high risk for violence or self-harm. Patients were also to be excluded if they had received an experimental drug or used an experimental medical device within 30 days prior to the planned start of treatment, had a narrowing or blockage of their gastrointestinal tract or were unable to take oral medications, or had a known hypersensitivity to paliperidone ER or risperidone. Patients with comorbid psychiatric disorders including substance abuse could be enrolled in this study, except those with a history of substance (including alcohol) dependence over the preceding 6 months.

2.3. Treatment

Paliperidone ER was initiated without titration at a dose intended to be effective, as selected by the treating clinician. The protocol recommended using 6 mg paliperidone ER once daily as a starting dose; however, dosing was based on treating clinicians' decision. Flexible dosing with paliperidone ER 3–12 mg/day was used throughout the study, with doses adjusted by investigators as clinically indicated. Flexible dosing was selected to more closely reflect treatment in routine clinical practice. In accordance with general treatment practice recommendations for acute situations (Kane et al., 2003), patients were required to be hospitalized for at least the first 7 days of the study.

Concomitant therapy with other antipsychotics and other psychotropic medication was permitted if these medications: (1) had been