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Effect of patient age on treatment response in a study of the acute exacerbation of psychosis in schizophrenia

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ABSTRACT

Younger patients with schizophrenia have most likely experienced fewer adverse consequences of the illness than older patients who may have experienced a lifetime of treatment as well as socio-economic problems as a consequence of the illness. There is limited information regarding differential efficacy of long-acting injectable (LAI) antipsychotic medications across the age span in patients with schizophrenia. We conducted a post hoc age and gender analysis of treatment response to aripiprazole lauroxil (AL; ARISTADA®; Alkermes, Inc.), in a 12-week, double-blind, placebo-controlled, multinational, Phase 3 study evaluating two doses of AL (441 mg and 882 mg) versus placebo in adult patients experiencing an acute exacerbation of schizophrenia within the previous 2 months. We examined change in the total Positive and Negative Syndrome Scale (PANSS) scores from baseline using analysis of covariance and categorical treatment response (defined as ≥30% total PANSS score improvement from baseline) in the following age groups: <30, 30–39, 40–49, and 50–69 years old. Age and gender did not moderate the treatment response in this study. Both AL 441 mg and AL 882 mg showed an early and significant improvement of the mean total PANSS scores and categorical treatment responses compared to placebo in all four age groups, including younger patients regardless of gender that was sustained over the 85-day treatment period.

1. Introduction

The onset of schizophrenia usually occurs in adolescence or early adulthood and generally continues throughout the lifetime of the individual (American Psychiatric Association, 1994; Hayes et al., 2012; US Department of Health and Human Services, 2015). The impact of schizophrenia on an individual's life depends in part on the severity and duration of the illness and the resulting social and economic consequences. A recently diagnosed 25-year-old patient will have had fewer psychotic episodes and less exposure to doctors, hospitals, and treatment interventions than a 55-year-old patient who may have experienced 30 or more years of evolving treatment interventions and providers as part of this chronic illness. Similarly, older patients with schizophrenia are more likely to experience adverse educational and socioeconomic consequences. It is conceivable that age-related experiential differences might influence expectations and affect the trajectory and/or robustness of response to antipsychotic treatment.

The eligibility criteria in most clinical trials of schizophrenia include patients between the ages of 18 and 65 (or 70) years regardless of their previous number of psychotic episodes, treatments, or other lifetime experiences. The 25-year-old and 55-year-old patients described above could be enrolled in the same trial and would be evaluated the same way in the statistical analysis plan.

Recently, several long-acting injectable (LAI) antipsychotic medications have been introduced that have been shown to reduce inpatient resource utilization by schizophrenic patients (Agid et al., 2010; Kane et al., 2013; Karson et al., 2013; Brissos et al., 2014; Kamat et al., 2015). In a 12-month follow-up study of 3094 Medicaid-insured patients with schizophrenia, Kamat et al. (2015) reported that LAIs reduced inpatient hospitalizations across all age groups analyzed. We recently conducted a 12-week clinical trial of the LAI aripiprazole lauroxil (AL; Aristada®; Alkermes, Inc.) in schizophrenic patients experiencing an acute exacerbation of psychosis (Meltzer et al., 2015). In that study (Meltzer et al., 2015), both AL 441-mg and AL 882-mg doses achieved an early and statistically significant benefit compared to placebo based on total score changes from baseline on the Positive and Negative Syndrome Scale (PANSS) that was sustained through 85 days of treatment (both doses vs. placebo at day 85: $p < 0.001$). In

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the present analysis, we examined whether age or gender were potential moderating factors on treatment outcome in the above mentioned clinical trial.

2. Experimental/materials and methods

Data were collected from a 12-week, Phase 3, multiregional, double-blind, placebo-controlled study in patients with schizophrenia (Clinicaltrials.gov identifier: NCT01469039) (Meltzer et al., 2015) that was conducted from December 2011 to March 2014 at 107 clinical trial sites in 7 countries located in North America, Europe, and Asia. The study was conducted in accordance with the Declaration of Helsinki (1964) and Good Clinical Practices as outlined by the International Conference on Harmonisation (1997).

AL is an LAI antipsychotic medication that is administered by deep intramuscular injection (Turncliff et al., 2014). An institutional review board or local ethics committee for each site approved the protocol, amendments, and consent forms, and all patients 7provided written informed consent before participation in the study.

The primary objective of the study was to determine the efficacy of AL in patients with schizophrenia experiencing an acute exacerbation of psychosis, as measured by change in total PANSS score (Kay et al., 1987) from baseline to day 85. Eligible patients aged 18 to 70 years of age met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria for schizophrenia based on the Structured Clinical Interview for DSM-IV Disorders – Clinical Trials (SCID-CT) and had experienced an onset of acute exacerbation of psychosis within the past 2 months (American Psychiatric Association, 1994; First et al., 2007). Eligible patients had a total PANSS score between 70 and 120, inclusive, and ≥ two of four key positive symptoms (delusions, conceptual disorganization, hallucinatory behavior, and suspiciousness) at least moderate in severity and a Clinical Global Impression–Severity (CGI-S) score ≥ 4 (moderate illness) at the screening and baseline visits (Guy, 1976). Patient selection included a site-independent review for diagnostic confirmation and symptom severity confirmation (Targum and Pendergrass, 2014). After randomization, efficacy assessments for the PANSS, CGI-S, and CGI-I (Improvement) scales were administered at days 8, 15, 22, 29, 57, and 85.

Eligible patients were admitted to an inpatient study unit, and currently prescribed antipsychotic medications were discontinued over 2–5 days prior to randomization. For patients who had never taken aripiprazole, a test dose of oral aripiprazole 5 mg was administered for 2 days before randomization, with the tolerability of the two test doses assessed. Patients who had previously taken and tolerated aripiprazole were not required to take these two test doses. Eligible patients were randomized in a 1:1:1 double-blind fashion to AL 441 mg (300-mg aripiprazole equivalent), AL 882 mg (600-mg aripiprazole equivalent), or placebo (a fat emulsion intralipid) and given a gluteal muscle injection every 4 weeks (days 1, 29, 57, and 85). The volumes of the AL 441-mg and AL 882-mg doses were different; therefore, patients who were randomized to placebo were further randomized (in a 1:1 ratio) to high- or low-volume placebo to maintain the blinded condition. Thus, the overall randomization ratio to AL 882 mg, AL 441 mg, placebo high volume, and placebo low volume was 2:2:1:1, respectively. In addition, patients assigned to either of the two AL treatment groups received oral aripiprazole (15 mg) daily for the first 3 weeks, whereas patients assigned to placebo received matching oral placebo. Patients remained in the inpatient unit for at least 2 weeks after the first administration of intramuscular medication and were discharged only if the investigator believed the patient was clinically stable.

In the present analysis, we examined treatment outcome by treatment group stratified by patient age at the time of the screening visit: <30 (18–29), 30–39, 40–49, and >50 (50–69) years and age as a continuous variable. The data analysis was based on the efficacy population (n = 596), defined as patients who received the study drug and had at least one post baseline PANSS assessment. In the earlier report of Meltzer et al. (2015), we reported data based on the safety population (n = 622).

Statistical analysis of the data included an analysis of covariance (ANCOVA) for last observation carried forward (LOCF) in the efficacy population. We also examined the categorical treatment response defined as an improvement (decrease) in total PANSS score by ≥30% from baseline.

3. Results

As previously reported (Meltzer et al., 2015), both AL 441 mg and AL 882 mg doses achieved an early and statistically significant benefit compared to placebo based on total PANSS score changes that was sustained through 85 days of treatment (both doses vs. placebo at day 85: $p < 0.001$). At the screen visit, 430 of the 596 patients in the efficacy population (72.1%) were taking an antipsychotic medication that was withdrawn within 2–5 days after that visit and prior to randomization. The withdrawal of prior antipsychotic medication had no effect on the treatment outcome in this sub-population, as both AL 441 mg and AL 882 mg doses were significantly better than placebo at day 85 ($p < 0.001$ for both doses versus placebo).

Patients in the efficacy population were stratified into four distinct age groups: <30 years (n = 128), 30–39 years (n = 170), 40–49 years (n = 165), and >50 years (n = 133).

Patients assigned to AL 441 mg or AL 882 mg were more likely to complete the study; 265 of the 400 (66.3%) completed the study in contrast to 95 of 196 (48.5%) patients assigned to placebo ($\chi^2 = 16.7$; degrees of freedom = 1; $p < 0.001$). Study completion rates in the AL study arms were similar across all four age groups. Fifty-four of 78 (69.2%) patients <30 years of age receiving either AL dose completed the study compared to 26 of 50 (52%) patients receiving placebo. Similarly, 71.1% of patients aged 30–39 years receiving either AL dose compared to 43% receiving placebo; 63.6% of patients aged 40–49 years receiving either AL dose compared to 55.3% receiving placebo; and 60.2% of patients aged >50 receiving either AL dose compared to 44% receiving placebo completed the study.

3.1. Age and efficacy

Age (assessed as a continuous variable) had no significant effect on treatment outcome based upon changes in the total PANSS score from baseline to day 85. AL 441 mg versus placebo (ANCOVA: $F = 0.27$; $p = 0.60$) and AL 882 mg versus placebo ($F = 0.92$; $p = 0.34$) revealed no significant age and treatment interaction effects.

Table 1 lists total PANSS scores at each visit through day 85 for the 4 stratified age groups by treatment assignment. As shown, patient age did not affect the clinically significant responses to either AL dose versus placebo. Figs. 1–4 depict the treatment response trajectories for each age group by treatment assignment. Patients <30 years of age showed an early response to either AL dose by day 8 that was sustained at every subsequent visit.

Patients <30 years of age who were assigned to placebo had a total mean PANSS score change of -2.86 ± 1.36 (standard error [SE]) at day 8 in contrast to -5.7 ± 0.93 in patients aged ≥30 years receiving placebo (LS mean difference [SE]: 3.07 ± 1.86; $p = 0.1$). The lower placebo response became equivalent with the other age groups by week 2 (day 15). The placebo response plateaued by the fourth treatment week (day 29) in all age groups and remained essentially unchanged for the remaining 2 months of the double-blind study.

Among patients aged >50 years assigned to placebo, the mean total PANSS score change from baseline occurred primarily in the first week of treatment and remained essentially unchanged after that until day 85 (Fig. 4). In contrast, in patients <50 years of age assigned to placebo, the mean total PANSS score change continued to improve for up to 4 weeks after randomization (Figs. 1–3). Although not statistically significant, patients aged >50 years tended toward a lesser overall mean