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Switching patients with schizophrenia from paliperidone palmitate to aripiprazole lauroxil: A 6-month, prospective, open-label study☆

Brian J. Miller [a,*], Amy Claxton [b], Yangchun Du [b], Peter J. Weiden [b], Steven G. Potkin [c]

[a] Department of Psychiatry and Health Behavior, Augusta University, Augusta, GA 30912, United States
[b] Clinical Development and Medical Affairs, Alkermes, Inc., Waltham, MA 02451, United States
[c] Department of Psychiatry and Human Behavior, University of California, Irvine, Irvine, CA 92697, United States

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ABSTRACT

We assessed the effectiveness of switching from paliperidone palmitate (PP) or risperidone long-acting injection (RLAI) to aripiprazole lauroxil (AL). Prospective, 6-month study in patients with schizophrenia with residual symptoms or intolerance with PP/RLAI. Effectiveness assessed via all-cause and medication-related discontinuation; CGI-S/BPRS and adverse event monitoring assessed efficacy/tolerability, respectively. Fifty-one patients ($n = 50$ PP; $n = 1$ RLAI) enrolled; 35 completed the study. All-cause and medication-related discontinuation was 30% and 9% over 6 months, respectively. CGI-S/BPRS improved significantly in those continuing treatment. Adverse events were generally mild to moderate. Patients with efficacy or tolerability concerns with PP/RLAI can be switched to AL.

1. Introduction

As the number of long-acting injectable antipsychotic medication options increases, the need has grown for commensurate data pertaining to safety and outcomes when switching between different LAIs (Correll et al., 2016). In particular, clinicians may hesitate to recommend a medication change because they are unsure about the relative safety of switching a patient from one long-acting injectable antipsychotic medication based on suboptimal response to another long-acting injectable with a different pharmacodynamic profile.

Paliperidone palmitate (PP) and risperidone LAI (RLAI) are widely used atypical long-acting injectable antipsychotics. Although PP and RLAI are effective, as with any first-line antipsychotics, PP and RLAI will not be fully effective or tolerable for all patients, and clinicians may consider switching to another LAI with a different pharmacodynamic profile. Aripiprazole lauroxil (AL), a prodrug of the atypical antipsychotic aripiprazole, is an long-acting injectable for the treatment of adults with schizophrenia (Citrome, 2016; Cruz, 2016). The objective of this study was to assess the clinical outcomes and safety of switching patients who continue to experience persistent symptoms or tolerability problems from PP/RLAI to AL.

2. Experimental methods

2.1. Study design

This was a prospective, 6-month, open-label study in patients with schizophrenia who were clinically stable on PP/RLAI but who continued to experience persistent symptoms or tolerability problems that may be addressed by a change in antipsychotic medication (ClinicalTrials.gov, NCT02634320; Fig. 1). The primary objective was to explore the treatment effectiveness, safety, and tolerability of AL in patients who had switched from PP/RLAI.

The first AL dose and subsequent dose adjustments were according to the investigator's clinical judgment. Stepwise dose decreases were allowed for tolerability, while increases were allowed for efficacy or up-titration. Most dose changes were performed after the second injection in accordance with protocol recommendations. Oral antipsychotics prescribed and administered at therapeutic levels before the start of the study could be continued at the investigator's discretion.

☆ Previous presentation: Study results have been presented as a poster at the 30th US Psychiatric and Mental Health Congress 2017 (New Orleans, LA, September 16–19).

* Corresponding author at: Department of Psychiatry and Health Behavior, Augusta University, 997 St. Sebastian Way, Augusta, GA 30912, United States.
E-mail addresses: BRMILLER@augusta.edu (B.J. Miller), amy.claxton@alkermes.com (A. Claxton), yangchun.du@alkermes.com (Y. Du), Peter.Weiden@alkermes.com (P.J. Weiden), sgpotkin@uci.edu (S.G. Potkin).

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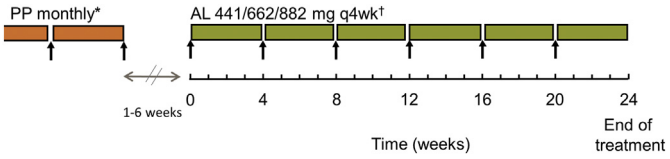

Fig. 1. Study design. Vertical arrows indicate PP monthly or AL q4wk administration. * Previous PP doses were in the range of 117–234 mg monthly; one patient previously received RLAI. † Flexibly dosed with q4wk injections occurring in weeks 4, 8, 12, 16, and 20. After the first injection, patients returned to the study site q4wk (441, 662, or 882 mg) or q6wk (882 mg only) for IM AL administration and outpatient assessments. Most patients (50 of 51) were on a q4wk AL regimen. ‡ Eligible patients must have demonstrated tolerability to oral aripiprazole (see text). Patients received their first dose of AL within 1 to 6 weeks after the last injection of the previous LAI. Administration of oral aripiprazole supplementation for 21 days with the initial dose of AL was at the discretion of the investigator. AL = aripiprazole lauroxil; IM = intramuscular; PP = paliperidone palmitate; RLAI = risperidone long-acting injection; qXwk = every 4 or 6 weeks.

2.2. Patients

Eligible participants were from 18 to 65 years of age with a diagnosis of schizophrenia as defined by the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) (American Psychiatric Association, 2013). Patients had to have been clinically stable for ≥2 months (no hospitalizations and Brief Psychiatric Rating Scale [BPRS] score ≥30 and ≤45), and had to have been treated with ≥3 doses of PP/RLAI before screening, with no antipsychotic medication regimen change for 4 weeks before day 1.

2.3. Outcome measures and assessments

A composite measure of treatment effectiveness was "all-cause discontinuation" (defined as discontinuation for any reason) (Lieberman et al., 2005) and "medication-related discontinuation" (defined as discontinuations specifically attributed to limitations of AL [i.e., due to lack of efficacy or an adverse event (AE)]).

Clinical symptoms were assessed using the Clinical Global Impressions–Severity (CGI-S; 7-point scale ranging from 1 [normal] to 7 [among the most extremely ill patients] (Guy, 1976)) and BPRS scores (18 items on which clinicians rate patients' symptoms on a 7-point scale (Overall and Gorham, 1962)) at baseline and monthly thereafter. Safety and tolerability was assessed by monitoring AEs.

2.4. Statistical analysis

The initial planned enrollment was 90 patients but the final enrollment included 51 patients because of enrollment challenges. Summary statistics (number, mean, and SD for continuous variables; number and percentage of patients in each category for categorical variables) are provided for variables evaluated.

Patient disposition and baseline demographics were summarized. Patients were categorized into three groups—persistent positive symptoms, persistent negative symptoms, and tolerability concerns—based on the primary reasons for switching at the time of study enrollment. Differences in baseline demographics and characteristics among the three groups were compared using analysis of variance for continuous outcomes and chi-square test for categorical outcomes.

Kaplan-Meier survival curves were used to estimate the time to discontinuation of treatment (all-cause and medication-related) in all enrolled patients. CGI-S and BPRS scores and change from baseline at each visit were summarized by switch group and overall using descriptive statistics. A one-sample *t*-test at each visit and at the end of the treatment period for all patients was conducted to determine whether changes from baseline were statistically significant. Changes in CGI-S and BPRS scores were also analyzed using a mixed-effects model for repeated measures (MMRM) for patients previously administered PP ($n = 50$) (excluding one patient previously treated with RLAI). These analyses included visits as factors and baseline values as covariates. The unstructured variance and covariance matrix was used to model within-subject variability. Least squares mean change from baseline and SE at each visit were reported and were compared for statistical significance on a 2-sided alpha level of 0.05.

3. Results

3.1. Patient disposition and baseline demographics

Fifty-one patients enrolled in the study and switched to AL from PP ($n = 50$) and RLAI ($n = 1$). Mean age was 40.6 years and most (72.5%) were men (Table 1). Primary reasons for switching patients from previous LAI to AL included persistent positive symptoms ($n = 34$; 66.7%), ongoing tolerability concerns ($n = 9$; 17.6%), and persistent negative symptoms ($n = 8$; 15.7%) (Fig. 2). Baseline characteristics were comparable between subgroups (Table 1), except for lower baseline CGI-S scores in the group who switched for tolerability reasons.

Table 1
Baseline demographics and characteristics.

Characteristic[a,b]	Reason for medication switch			All patients $N = 51$
	Persistent positive symptoms $n = 34$	Persistent negative symptoms $n = 8$	Tolerability concerns $n = 9$	
Age, years	40.6 (11.9)	40.5 (10.3)	41.1 (13.7)	40.6 (11.7)
Male, *n* (%)	24 (70.6)	7 (87.5)	6 (66.7)	37 (72.5)
Primary race, *n* (%)				
Black or African American	15 (44.1)	3 (37.5)	7 (77.8)	25 (49.0)
White	16 (47.1)	4 (50.0)	2 (22.2)	22 (43.1)
Asian	3 (8.8)	0	0	3 (5.9)
Other	0	1 (12.5)	0	1 (2.0)
BMI, kg/m^2	31.8 (6.2)	31.9 (10.6)	30.6 (3.6)	31.6 (6.6)
Duration of previous long-acting injectable antipsychotic use, months	15.1 (19.3)	20.9 (20.7)	8.6 (11.3)	14.9 (18.4)
Concomitant oral antipsychotic use, *n* (%)	13 (38.2)	2 (25.0)	1 (11.1)	16 (31.4)
BPRS total score	38.7 (6.37)	34.6 (2.97)	36.1 (3.82)	37.6 (5.74)
CGI-S score	4.1 (0.60)	3.9 (0.35)	3.3 (0.50)	3.9 (0.61)

BMI = body mass index; BPRS = Brief Psychiatric Rating Scale; CGI-S = Clinical Global Improvement-Severity Scale.
[a] All values presented as mean (SD) unless otherwise indicated.
[b] No statistically significant differences in baseline demographics and characteristics among the three groups except for CGI-S score ($p = 0.004$).