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ORIGINAL RESEARCH

Effects of aripiprazole once-monthly on symptoms of schizophrenia in patients switched from oral antipsychotics

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Objective. To assess the effects of aripiprazole once-monthly 400 mg (AOM 400) on clinical symptoms and global improvement in schizophrenia after switching from an oral antipsychotic.

Methods. In a multicenter, open-label, mirror-image, naturalistic study in patients with schizophrenia (>1 year, *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision [DSM-IV-TR] criteria), changes in efficacy measures were assessed during prospective treatment (6 months) with AOM 400 after switching from standard-of-care oral antipsychotics. During prospective treatment, patients were cross-titrated to oral aripiprazole monotherapy (1–4) weeks followed by open-label AOM 400 (24 weeks). Mean change from baseline of the open-label AOM 400 phase in Positive and Negative Syndrome Scale (PANSS) scores (total, positive and negative subscales) and Clinical Global Impression–Severity (CGI-S) scores; mean CGI–Improvement (CGI-I) score; and proportion of responders (≥30% decrease from baseline in PANSS total score or CGI-I score of 1 [very much improved] or 2 [much improved]) were assessed.

Results. PANSS and CGI-S scores improved from baseline ($P < 0.0001$) and CGI-I demonstrated improvement at all time points. By the end of the study, 49.0% of patients were PANSS or CGI-I responders.

Conclusions. In a community setting, patients with schizophrenia who were stabilized at baseline and switched to AOM 400 from oral antipsychotics showed clear improvements in clinical symptoms.

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Key words: Antipsychotic agent, aripiprazole once-monthly, long-acting injectable, naturalistic study, schizophrenia.

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Trial registry: ClinicalTrials.gov NCT01432444 http://clinicaltrials.gov/show/NCT01432444.

Introduction

The chronic nature of schizophrenia requires long-term treatment to prevent relapse and maintain functioning and symptom control.[1–4] Nonadherence to and lack of persistence to treatment with antipsychotic therapy are common in patients with schizophrenia. A recent nationwide survey revealed that more than one-half of patients with schizophrenia were nonadherent to their antipsychotic therapy.[5] Nonadherence in schizophrenia is associated with many negative clinical and patient-rated outcomes, including an increased risk of psychiatric

hospitalization, being arrested, poorer mental functioning, and lower levels of life satisfaction compared with adherent patients.[6,7] Common reasons for nonadherence to antipsychotic therapy in patients with schizophrenia include lack of insight, medication side effects (eg, weight gain, sexual dysfunction), lack of treatment efficacy or social support to help with treatment adherence, and complex treatment regimens.[4] Nonadherent patients with schizophrenia who were prescribed oral antipsychotics may benefit from a treatment that minimizes the daily burden of their regimen, such as a long-acting injectable (LAI) antipsychotic.[8] Multiple studies have shown that switching from oral to LAI antipsychotics significantly reduced hospitalization rates,[9–12] which can minimize disruptions to employment or school and reduce healthcare-related costs.

Aripiprazole once-monthly 400 mg (AOM 400) is a LAI formulation of aripiprazole used for the treatment of schizophrenia. The safety and efficacy of AOM 400 in preventing relapse in patients with schizophrenia was demonstrated in 2 long-term, randomized, double-blind, placebo or active-controlled studies in which AOM 400 significantly delayed time to impending relapse and impending relapse rate compared with placebo or a subtherapeutic dose of AOM.[13,14] Efficacy and safety in the treatment of patients with schizophrenia experiencing an acute psychotic episode were also demonstrated in a randomized, double-blind, placebo-controlled study in which AOM 400 significantly improved symptoms and functioning compared with placebo.[15]

Efficacy as assessed in randomized, controlled trials does not always reflect real-world effectiveness in clinical practice for reasons such as low adherence rates or less stringent or thorough guidance on initiating and titrating therapy.[16] For example, a recent meta-analysis of randomized, controlled trials comparing the efficacy and safety of long-acting injectables versus oral antipsychotics in patients with schizophrenia found comparable efficacy between formulations in reducing relapse.[17] In contrast, a meta-analysis of naturalistic, mirror-image studies in patients with schizophrenia found superior efficacy of long-acting injectables in preventing hospitalizations.[11] We have previously confirmed that rates of hospitalizations were significantly reduced after patients switched from oral antipsychotics to AOM 400 in an open-label, naturalistic, mirror-image study in a community setting.[10] To further assess the effects of switching from oral antipsychotics, including oral aripiprazole, to AOM 400 in a naturalistic setting, we examined secondary efficacy outcomes of clinical symptoms and clinical global improvements in patients with schizophrenia from the same study.

Methods

Patients

Patient inclusion and exclusion criteria were previously described.[10,18] Briefly, patients eligible for study inclusion were aged 18–65 years old, had ≥1 year duration of schizophrenia based on the *Diagnostic of Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR), were treated with oral antipsychotic therapy throughout the 7-month retrospective period prior to screening, and had ≥1 psychiatric inpatient hospitalization within 4 years preceding study screening but were managed as stable outpatients during the 4 weeks prior to signing the informed consent form and throughout the screening period. Patients who, in the investigators' opinion, required a change in treatment for any reason (eg, lack of efficacy, history of nonadherence, adverse events) and who would potentially benefit from switching to maintenance treatment with a long-acting injectable antipsychotic were considered for study inclusion. Patients with DSM-IV-TR diagnoses other than schizophrenia and patients with a history of aripiprazole intolerance or lack of response were excluded from study enrollment.[10]

Study design

Details regarding study design were previously described.[10,18] Briefly, this multicenter, open-label, naturalistic, single-treatment, mirror-image study was conducted in North American communities (NCT01432444) and was approved by study sites' ethics committees as set forth in the Declaration of Helsinki.[10] Patients provided informed consent, and eligibility was assessed during the screening phase (days 2–28). Antipsychotic medication data were obtained for the 7 months prior to screening. The oral conversion phase (Phase A, 1–4 weeks), in which patients initiated oral aripiprazole 10–30 mg prior to AOM 400, was flexible: study investigators could taper patients off other oral antipsychotics during the screening phase, prior to initiating oral aripiprazole, or they could cross-titrate with oral aripiprazole during Phase A. Patients who had a prior history of tolerance to oral aripiprazole could directly enter the prospective 6-month open-label AOM 400 treatment phase (Phase B), during which patients were treated with AOM 400 and concomitant oral aripiprazole for the first 14 days. During the open-label AOM 400 treatment phase, a dose reduction to 300 mg was permitted if patients experienced tolerability issues. Patients were assessed at baseline (week 0) and through week 24[10] (Figure 1).

Endpoints

As previously reported, the primary endpoint, a comparison of the proportion of patients who had ≥ 1 inpatient psychiatric hospitalization during standard-of-care

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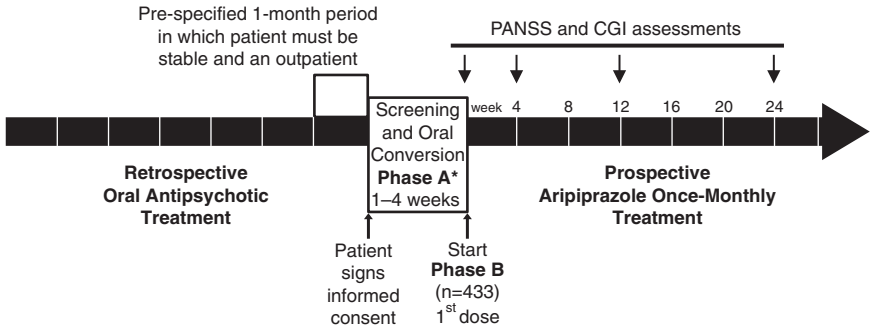

FIGURE 1. Study design. *Patients who were already receiving oral aripiprazole treatment entered the open-label treatment phase (Phase B) without entering the oral conversion phase (Phase A). CGI = Clinical Global Impression; PANSS = Positive and Negative Syndrome Scale. Modified and reprinted with permission from Kane JM, *et al.* Hospitalization rates in patients switched from oral anti-psychotics to aripiprazole once-monthly: final efficacy analysis. *J Med Econ.* 2015;**18**(2):145–154.

oralantipsychotic treatment (months -4 to -1 of the retrospective period) versus during AOM 400 treatment (months 4–6 of the prospective treatment period) favored AOM 400 (27.1% [n = 91/336] vs 2.7% [n = 9/336], respectively; $P < 0.0001$).[10] Secondary efficacy outcomes of clinical symptoms and clinical global improvements were assessed during the prospective period with the Positive and Negative Syndrome Scale (PANSS) total score and positive and negative subscale scores,[19] Clinical Global Impressions–Severity of Illness (CGI-S) scale,[20] and Clinical Global Impressions–Global Improvement (CGI-I) scale.[21] The proportion of responders, defined a priori as patients who achieved a ≥30% reduction from baseline in PANSS total score or a score of 1 (very much improved) or 2 (much improved) on the CGI-I, was calculated. Efficacy endpoints were assessed in the prospective period only, and baseline values were defined as the last assessment prior to or on the date of the first AOM 400 dose (ie, last assessment in Phase A or first assessment in Phase B prior to AOM 400 initiation).

Statistical analyses

Mean changes from baseline to week 24 in PANSS total, PANSS positive and negative subscales, and CGI-S scores; mean CGI-I score at week 24; and the proportion of responders were analyzed at weeks 4, 12, and 24 in the last observation carried forward (LOCF) and observed case (OC) data sets using paired *t*-tests and/or descriptive statistics. Missing data were imputed for the LOCF dataset using the most recent assessment prior to the missed observation; baseline values were not carried forward. Analyses were examined in the intent-to-treat dataset, which included all patients who entered Phase B. No correction for multiple testing was performed.

Results

Patient disposition was described in detail previously.[10] Briefly, 800 patients were screened, and 493 met study eligibility and enrolled.[10] For Phase B, 433 patients entered and 431 received ≥1 AOM 400 injection; 69.1% of patients received all 6 AOM injections, and 67.7% of patients completed Phase B. During phase B, 8.5% of patients discontinued due to adverse events (AEs). The majority of patients in Phase B were male (n = 301/433), and the mean ± SD age was 42.1 ± 12.0 years (Table 1). At Phase B baseline, mean ± SD disease severity was moderate (CGI-S, 3.7 ± 0.8, and PANSS, 75.0 ± 18.3).

TABLE 1. Demographics and baseline characteristics in Phase B

Demographic or Characteristic	Phase B (n = 433)
Age, mean (SD), y	42.1 (12.0)
Men/women, n	301/132
Body weight, mean (SD), kg*	91.2 (21.2)
BMI, mean (SD), kg/m^2*	30.8 (7.1)
Race, n (%)	
White	216 (49.9)
Black	198 (45.7)
American Indian or Alaska Native	3 (0.7)
Asian	10 (2.3)
Other	6 (1.4)
Ethnicity	
Hispanic or Latino	94 (21.7)
Not Hispanic or Latino	339 (78.3)
PANSS total score, mean (SD)†	75.0 (18.3)
Conceptual disorganization (P2)	2.8 (1.2)
Suspiciousness (P6)	3.2 (1.1)
Hallucinatory (P3)	3.0 (1.4)
Unusual thought content (G9)	2.6 (1.1)
CGI severity score, mean (SD)‡	3.7 (0.8)
Age at first diagnosis, mean (SD), y†	26.7 (10.5)

BMI = body mass index; CGI = Clinical Global Impressions; PANSS = Positive and Negative Syndrome Scale.

*n = 422.

†n = 427.

‡n = 425.

Data represent all patients who enrolled in the study phase. Modified and reprinted with permission from Kane JM, *et al.* Hospitalization rates in patients switched from oral anti-psychotics to aripiprazole once-monthly: final efficacy analysis. *J Med Econ.* 2015;**18**(2):145–154.

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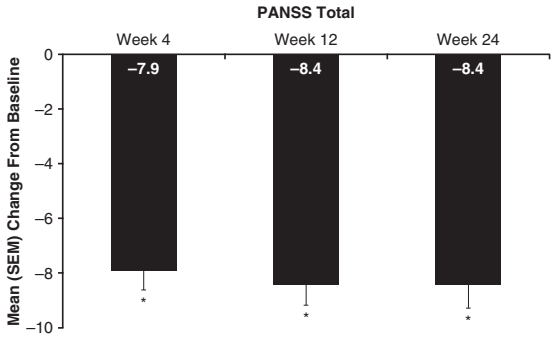

FIGURE 2. Change from baseline in PANSS total score following the switch to AOM 400 treatment. *$P < 0.0001$. Last observation carried forward analyses in Phase B efficacy sample (N = 431). Error bars denote standard error. AOM 400 = aripiprazole once-monthly 400 mg; baseline = Phase B baseline.

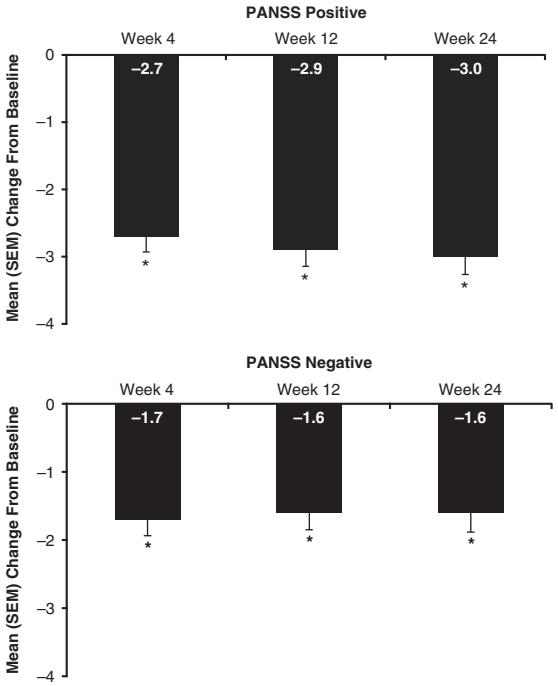

FIGURE 3. Change from baseline in PANSS positive and negative subscales following the switch to AOM 400 treatment. *$P < 0.0001$. Last observation carried forward analyses in Phase B efficacy sample (N = 431). AOM 400 = aripiprazole once-monthly 400 mg; baseline = Phase B baseline.

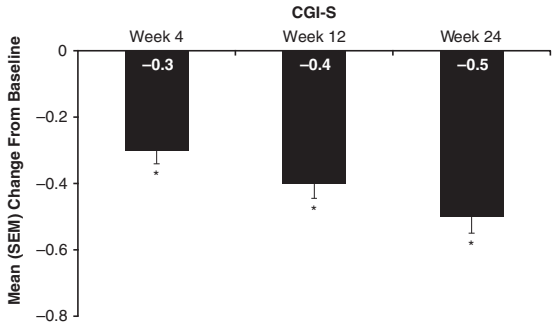

FIGURE 4. Change from baseline in CGI-S scores following the switch to AOM 400 treatment. *$P < 0.0001$. Last observation carried forward analyses in Phase B efficacy sample (N = 431). AOM 400 = aripiprazole once-monthly 400 mg; baseline = Phase B baseline.

Oral antipsychotics used during the retrospective period (ie, prior to phase A and prior to initiating AOM 400) included amisulpride, aripiprazole, asenapine, cariprazine, chlorpromazine, clozapine, flupentixol, fluphenazine, haloperidol, iloperidone, loxapine, lurasidone, olanzapine, paliperidone, perphenazine, pimozide, quetiapine, risperidone, thioridazine, thiothixene, trifluoperazine, and ziprasidone.

Mean PANSS total scores improved at all time points (ie, weeks 4, 12, and 24) following initiation of AOM 400 ($P < 0.0001$ vs baseline at all time points; Figure 2). Likewise, mean PANSS positive and negative subscale scores were reduced (improved) at weeks 4, 12, and 24 ($P < 0.0001$ vs baseline at all time points; Figure 3). Results from the OC analyses for PANSS total scores and positive and negative subscale scores were consistent with the LOCF analyses ($P < 0.0001$ vs baseline at all time points).

Mean CGI-S scores also improved from baseline at weeks 4, 12, and 24 ($P < 0.0001$ at all time points; Figure 4), and results from the OC analyses were consistent with the LOCF analyses ($P < 0.001$ at all time points). Mean ± SD CGI-I scores were comparable at week 4 (3.0 ± 1.0), week 12 (2.9 ± 1.1), and week 24 (2.8 ± 1.2), indicating that, on average, at all time points, investigators rated patients as improved compared to phase B baseline. Mean ± SD CGI-I scores from the OC dataset were also comparable across study weeks (week 4, 3.0 ± 1.0; week 12, 2.7 ± 1.1; week 24, 2.5 ± 1.1).

The proportion of PANSS or CGI-I responders increased from week 4 through the end of the study (Figure 5). Considering PANSS and CGI-I separately, the proportion of patients with ≥30% improvement in PANSS total score increased from 10.8% to 12.9% and 16.1% at weeks 4, 12, and 24, respectively. In looking at CGI-I alone, the proportion of patients scoring 1 or 2 increased from 30.6% to 40.0% and 45.4% at weeks 4, 12, and 24, respectively.

The safety and tolerability of AOM 400 in the current study were previously reported[10] and were consistent with the AOM 400 randomized, controlled trials for the maintenance treatment of patients with schizophrenia[13,14] and for the treatment of acute exacerbations of psychotic symptoms in patients with schizophrenia.[15] The most common treatment-emergent adverse events (TEAEs) in phase B (≥5%) were insomnia (n = 29, 6.7%) and akathisia (n = 28, 6.5%).[10]

Discussion

Switching from oral antipsychotics, including oral aripiprazole, to AOM 400 reduced clinician-rated

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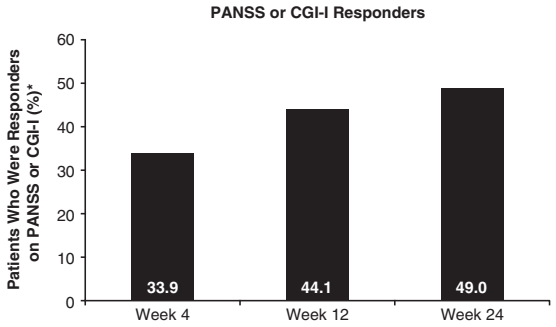

FIGURE 5. Proportion of patients meeting PANSS or CGI-I responder criteria. * ≥ 30% decrease from baseline in PANSS total score or CGI-I score of 1 (very much improved) or 2 (much improved). Last observation carried forward analyses in Phase B efficacy sample (week 4, N = 389; week 12, N = 410; week 24, N = 410).

symptom severity in patients with schizophrenia who were stable (ie, outpatients for ≥4 weeks prior to study enrollment and throughout the screening period and did not require inpatient hospitalization during phase A) and mild to moderately ill at baseline (mean CGI-S, 3.7). Improvements from baseline were noted as early as week 4 (ie, after 1 injection), and consistently at weeks 12 and 24 on the PANSS total score, PANSS positive and negative subscales, and CGI-S score. On average, clinicians noted overall improvements in patients after switching from oral antipsychotics to AOM 400, with mean CGI-I scores after AOM 400 initiation ranging from 2.5 to 3.0 (2 = much improved, 3 = minimally improved). Despite being stable at baseline, one-third of patients were responders at 4 weeks (ie, after the first injection), and the proportion of responders increased to nearly one-half by week 24. Two-thirds of patients who entered Phase B (prospective AOM 400 treatment) completed this 24-week treatment phase. The most frequently reported TEAEs were akathisia and insomnia, and the AE profile in this naturalistic, community study was consistent with those in randomized, controlled trials of AOM 400 in patients with schizophrenia.[13–15] Discontinuations due to AEs were low (8.5%) during AOM 400 treatment.[10]

Our results are distinctive in that we now report efficacy outcomes other than hospitalization rates from a mirror-image, naturalistic study with AOM 400 in patients with schizophrenia. Our findings support the results for the primary study endpoint, which demonstrated significantly lower psychiatric hospitalization rates during months 4–6 of prospective AOM 400 treatment compared to the 3 months prior to AOM 400 treatment (ie, during retrospective standard of care treatment with oral antipsychotics). Our findings are also consistent with a 6-month, open-label, mirror-image study of patients who switched from oral olanzapine to risperidone LAI (RLAI) for similar reasons (ie, they had an insufficient treatment response, treatment side effects, adherence issues, and/or requested a treatment change). Six months after switching to RLAI, patients demonstrated significant improvements from baseline on PANSS total and Marder factor scores, and CGI-S scores ($P < 0.0001$). Similar to our study, approximately one-half of patients who switched to RLAI achieved ≥30% improvement from baseline on the PANSS total score.[22]

The generalizability of our findings may be limited to stable outpatients, and the naturalistic open-label design lacks the rigor and standardization of a randomized, double-blind, controlled trial with a comparator group.[10] The improvements on PANSS and CGI scores and high response rate may be indicative of improvements in medication adherence in this sample of patients who were relatively stable at baseline. For efficacy endpoints, mean changes from baseline to timepoints prior to week 24 were not pre-specified in the statistical analysis plan; statistically significant differences in PANSS total and subscale scores and CGI-S scores at these timepoints may reflect type 1 errors. Also, during the first 2 weeks of open-label AOM 400 treatment, study physicians had the option to initiate and titrate oral aripiprazole based on their clinical judgment (although the recommended starting dose was 10 or 15 mg/day and the upper limit for titration was 30 mg/day).[10] Lack of standardized oral aripiprazole dosing during the first 2 weeks may hinder the interpretability of findings at week 4, but variability in dosing procedures is also consistent with real-world clinical practice.

Conclusion

Results from this community setting support the primary efficacy analysis (significantly lower hospitalization rates after switching to AOM 400), and they also demonstrate that stable patients with schizophrenia can switch from an oral antipsychotic to AOM 400 and experience improvements on validated clinician-rated assessments of symptom severity and global improvement. Taken together, findings from the primary and secondary analyses support potential cost savings with reduced hospitalizations and clinical improvements in symptom severity.

Disclosures

Timothy Peters-Strickland, Cathy Zhao, Pamela P. Perry, Brian R. Johnson, Phyllis M. Salzman, Robert D. McQuade, and Raymond Sanchez are employees of Otsuka Pharmaceutical Development & Commercialization, Inc. Anna Eramo is an employee of Lundbeck LLC. This study and the development of this manuscript were supported by Otsuka Pharmaceutical Development & Commercialization, Inc and H. Lundbeck A/S.

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