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ORIGINAL PAPER

Descriptive analyses of the aripiprazole arm in the risperidone long-acting injectable versus quetiapine relapse prevention trial (ConstaTRE)

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Abstract A recent randomized, open-label, relapse prevention trial (ConstaTRE) compared outcomes with risperidone long-acting injectable (RLAI) versus the oral atypical antipsychotic quetiapine. This study also included a small descriptive arm in which patients could also be randomized to aripiprazole. Results of this exploratory analysis are described here. Clinically stable adults with schizophrenia or schizoaffective disorder previously treated with oral risperidone, olanzapine, or an oral conventional antipsychotic were randomized to RLAI or aripiprazole. Efficacy and tolerability were monitored for up to 24 months. A total of 45 patients were treated with aripiprazole (10–30 mg/day) and 329 patients with RLAI (25–50 mg i.m. every 2 weeks). Relapse occurred in 27.3% (95% CI: 15.0–42.8%) of aripiprazole-treated and 16.5% (95% CI: 12.7–21.0%) of RLAI-treated patients. Kaplan–Meier estimates of mean (standard error) relapse-free period were 313.7 (20.4) days for aripiprazole and 607.1 (11.4) days for RLAI patients. Remission was achieved by 34.1% (95% CI: 20.5–49.9%) of aripiprazole and 51.1% (95% CI: 45.5–56.6%) of RLAI patients. Clinical global impression–change was improved ("minimally improved" to "very much improved") in 26.4% with RLAI and 15.9% with aripiprazole patients. Tolerability was generally good for both treatment groups. Weight gain (7.0% with RLAI vs. 4.4% with aripiprazole), extrapyramidal adverse events (AEs) (10.3% vs. 4.4%), and potentially prolactin-related AEs (4.6% vs. 0%) were more common with RLAI treatment, and gastrointestinal disorders were more common in aripiprazole-treated patients (22.2% vs. 6.1%). Time-to-relapse in stable patients with schizophrenia or schizoaffective disorder was numerically longer in RLAI-treated patients than in aripiprazole-treated patients although not statistically significant. Both treatments were generally well tolerated.

Keywords Antipsychotic · Atypical · Relapse · Schizoaffective disorder—schizophrenia

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Introduction

Schizophrenia is a chronic, disabling disease that often requires long-term treatment. Effective long-term symptom improvement is frequently complicated by relapse [1]. Over the course of their illness, 80–85% of patients with schizophrenia will experience at least one relapse [2].

Medication nonadherence affects nearly half of all outpatients with schizophrenia treated for 1 year [3] and is a major risk factor for relapse [4].

A variety of atypical antipsychotics have demonstrated good efficacy for treating symptoms of schizophrenia and schizoaffective disorders. The atypical antipsychotic agent aripiprazole has been shown in clinical trials to be effective and well tolerated, with a low propensity for extrapyramidal symptoms and no clinically significant weight gain, hyperprolactinemia, or QT_c-interval prolongation [5]. In a recent analysis of five short-term studies treating schizophrenia or schizoaffective disorder, aripiprazole showed comparable efficacy to oral risperidone and haloperidol [6]. Furthermore, symptom maintenance and prevention of relapse were similar between aripiprazole and other antipsychotics, including haloperidol, olanzapine, quetiapine, and risperidone [6]. Another analysis of data from double-blind studies evaluated relapse in 14 long-term studies [7]. Among those studies evaluating aripiprazole, risk of relapse was likewise reported to be similar between aripiprazole and first-generation antipsychotics.

Despite good efficacy demonstrated in controlled clinical trials with antipsychotics, successful outcomes with oral therapies are limited by treatment partial or nonadherence. A variety of factors contribute to antipsychotic nonadherence, including poor medication tolerability, lack of insight, health beliefs, problems with treatment access, embarrassment/stigma over illness, patient or family opposed to medications, poor therapeutic alliance, complicated treatment regimen, cognitive dysfunction, and lack of social support [8–12].

Medication nonadherence may be reduced by treating patients with long-acting injectable antipsychotic formulations [4, 13, 14]. Currently available atypical long-acting injectable antipsychotics include risperidone long-acting injectable (RLAI), olanzapine long-acting injectable, and very recently paliperidone palmitate. Most data are available for RLAI. An open-label, 50-week RLAI study has evaluated remission rates in stable patients converted to RLAI treatment [15]. Among the 32% of patients who entered the study in remission, 85% maintained remission after conversion to RLAI. Among the 68% of patients who had not met remission criteria at baseline, 21% achieved remission after switching to RLAI.

ConstaTRE, a randomized controlled, open-label, relapse prevention trial of RLAI versus oral treatment with quetiapine or aripiprazole has recently been completed [16]. This study was designed to evaluate maintenance of effect (as measured by time-to-relapse) over 2 years in patients treated with RLAI or oral atypical antipsychotics quetiapine or aripiprazole in general psychiatric services across Europe. The primary analysis was a comparison between RLAI and quetiapine. For that primary analysis ($N = 329$ RLAI and $N = 337$ quetiapine), relapse occurred in 16.5% of patients treated with RLAI and 31.3% with quetiapine [16]. Time-to-relapse was significantly longer with RLAI ($P < 0.0001$). The 25th quartile of time-to-relapse was 248 days with quetiapine and could not be defined for RLAI as 25% of patients did not relapse by study endpoint. The current study describes a smaller explorative arm of the ConstaTRE study in which patients could also be randomized to aripiprazole. This report provides a descriptive analysis of the aripiprazole-treated patients compared with patients treated with RLAI.

Methods

Study design

This multicenter, open-label, randomized, active-control 2-year study comparing RLAI and oral quetiapine and aripiprazole was conducted from October 2004 to November 2007 at 124 sites in 25 countries (ClinicalTrials.gov identifier: NCT00216476). The primary analysis in this study was a comparison of efficacy maintenance between patients treated with RLAI and oral quetiapine. The aripiprazole-treated arm was included as a limited third comparative sample, to be assessed as a secondary explorative analysis. Aripiprazole-treated patients were only enrolled in countries where aripiprazole was commercially available, resulting in enrollment at 26 sites in 8 countries. This trial was conducted in accordance with the guidelines of the International Conference on Harmonization for Good Clinical Practice, and the study protocol and consent were approved by an Institutional Review Board. Informed consent was obtained on all patients prior to study enrollment.

Patients

Adults aged ≥18 years with schizophrenia or schizoaffective disorder diagnosed according to Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM–IV) criteria [17] were eligible to participate in this trial if they were symptomatically stable; were currently treated with monotherapy with oral risperidone ≤6 mg daily, oral olanzapine ≤20 mg daily, or an oral conventional neuroleptic (≤10 mg haloperidol daily or its equivalent); and were candidates for switching therapy due to insufficient symptomatic control, side effects, or patient request. Patients were considered to be clinically stable if the investigator judged them to be symptomatically stable; they had been using a stable dose of antipsychotic medication for ≥4 weeks prior to enrollment; and were living at the same residence for ≥30 days. Both stable outpatients and inpatients could be eligible for participation. Female

patients were required to be surgically sterile or practicing accepted contraception (e.g., prescription oral contraceptives, contraceptive injections, intra-uterine device, double-barrier method, contraceptive patch, male partner sterilization, or abstinence) and have a negative pregnancy test at baseline. Patients were excluded if they had a DSM–IV axis I diagnosis other than schizophrenia or schizoaffective disorder; were treated with antipsychotics other than oral risperidone, oral olanzapine, or oral conventional neuroleptics; or had been determined to be nonresponders to previous treatment with risperidone, quetiapine, aripiprazole, or ≥2 antipsychotics. Patients were also excluded if they were treated with mood stabilizers or antidepressants and had not received a stable dose for ≥3 months prior to study entry. Patients with phenylketonuria, severe drug hypersensitivity, drug or alcohol dependence, or suicide risk or attempt(s) were additionally excluded.

Treatment

Eligible patients were switched to randomly-assigned, open-label treatment with RLAI or oral quetiapine or aripiprazole for a maximum of 24 months. A stratified randomization according to previous treatment was used to ensure comparability of treatment arms with regard to previous treatment. Three strata were used: oral risperidone (40%), olanzapine (30%), and conventional oral neuroleptics (30%). Within each stratum, patients were randomly allocated on a 1:1 ratio to RLAI or quetiapine in countries where aripiprazole was not available, or 2:2:1 to RLAI, quetiapine, and aripiprazole in countries where aripiprazole was available. Dosing recommendations followed approved dosing guidelines for each study drug. Information on quetiapine has been presented elsewhere [16] and will therefore not be presented in the current report.

RLAI was initiated with 25 mg injections administered every 2 weeks, with patients continuing pre-study oral antipsychotic medication (oral risperidone, olanzapine, or conventional neuroleptic) for the first 3 weeks of RLAI treatment to ensure adequate antipsychotic coverage until the main release of risperidone from RLAI was expected, to achieve adequate drug plasma levels. After 3 weeks, the baseline oral antipsychotic was tapered off over 1–2 weeks. Patients randomized to RLAI with no history of risperidone exposure received 2 mg oral risperidone daily for 2 days prior to the first RLAI injection to assess tolerability. RLAI dosage could be increased in increments of 12.5 mg for patients experiencing worsening of psychotic symptoms or insufficient efficacy up to the maximum approved dose of 50 mg every 2 weeks. Increases were only permitted to occur during scheduled visits and after a minimum of 4 weeks after a previous change in the RLAI dose. RLAI dosage could be decreased as needed due to adverse events (AEs) at the treating physician's discretion.

Patients randomized to aripiprazole were treated with the usual recommended maintenance dosages of 10–30 mg daily, with dosage adjustments permitted as clinically indicated. Antipsychotics used prior to randomization were tapered off over 2 weeks, starting after first administration of aripiprazole. Adherence was monitored by evaluating the amount of study medication returned, using pill counts.

The need for a dose of study medication that exceeded the maximum approved maintenance dose or the addition of supplemental antipsychotic agents to control disease symptoms led to discontinuation of study medication, with the patient considered to have relapsed because symptoms were no longer sufficiently controlled by the study medication.

Patients using stable doses of mood stabilizers or antidepressants for ≥3 months prior to enrollment continued these medications after study drug initiation. Changes in dosage or initiation of a mood stabilizer or antidepressant were permitted during this study, if clinically necessary. Anticholinergic medication and benzotropine mesylate were permitted to treat extrapyramidal symptoms. Sedatives were generally avoided, with the exception of benzodiazepines for sleep. Lorazepam could be used for agitation as needed, with a maximum dose of 4 mg/day, during no more than 4 days in any 7-day period. In countries where lorazepam was not available, oral diazepam could be used instead, with a conversion of 10 mg of diazepam for every 1 mg of lorazepam allowed.

Assessments

Patient demographics, disease characteristics, and a physical examination were obtained at the initial screening visit. A baseline visit was scheduled within 2 weeks after the screening visit for additional assessments of weight, height, and symptom severity. During titration and throughout the study, scheduled nursing assessments occurred every 2 weeks (at the time of RLAI injection or over the telephone for patients randomized to aripiprazole). If a patient's psychotic condition had a negative change, an unscheduled additional visit was made. Scheduled follow-up appointments were conducted after 1 and 3 months, and then every 3 months for up to 2 years. In addition, patients were assessed by a nurse every 2 weeks throughout treatment to monitor for any change in patient status that would suggest an unscheduled visit was necessary; this assessment occurred in conjunction with RLAI administration or over the phone for patients randomized to aripiprazole treatment.

The positive and negative syndrome scale (PANSS), Montgomery–Asberg depression rating scale (MADRS),

and clinical global impression (CGI) were obtained at baseline and each subsequent visit. The primary assessment was the time from randomization to relapse. Relapse was defined using criteria utilized in a previous risperidone comparative study [18]. In order to be considered as having relapsed, the patient had to meet ≥1 of the following criteria on two consecutive evaluations, 3–5 days apart (the first of these visits was considered as the moment of relapse): psychiatric hospitalization; increase in level of care necessary and ≥25% increase in PANSS total score from baseline or an increase of 10 points if PANSS baseline score was ≤40; significant clinical deterioration defined as a CGI–change (C) score of 6 (much worse) or more; deliberate self-injury; emergence of clinically significant suicidal or homicidal ideation; violent behavior resulting in significant injury to another person or property; exceeding the registered dose of the drug (50 mg every 2 weeks for RLAI or 30 mg daily for aripiprazole).

Secondary efficacy outcome measures included achievement and maintenance of remission and change in PANSS total and subscale scores, PANSS factors based on Marder [19], MADRS scores, and CGI–severity (S) and CGI–C scores. Remission was defined using criteria proposed by the remission in schizophrenia working group [20] which was used in previous long-term studies [21, 22]. Patients were identified as having achieved remission if they scored ≤3 on all 8 key PANSS items for: negative symptoms (blunted affect, passive/apathetic social withdrawal, and lack of spontaneity and flow of conversation), disorganization (conceptual disorganization and manner-isms/posturing), and psychoticism (delusions, unusual thought content, and hallucinatory behavior), with these severity criteria achieved and maintained continuously for ≥6 months.

Functional status was measured at baseline and every 6 months using the social and occupational functioning assessment scale (SOFAS), which provides information on an individual's social and occupational functioning, with possible scores ranging from 1 ("severe impairment") to 100 ("excellent function") [17]. Clinicians applying the SOFAS to patients were instructed to consider only impairments that were a direct consequence of mental or physical conditions and not the result of environmental or opportunity limitations. Functional impairment from general medical conditions is also considered when rating function with the SOFAS.

Quality-of-life was assessed at baseline and treatment months 1, 3, 6, 12, 18, and 24 with the medical outcomes survey short-form 12 (SF-12) and the schizophrenia quality-of-life scale–revision 4 (SQLS–R4). The SF-12 is a 12-item subset of the medical outcomes survey SF-36, with good correlation to the SF-36 [23]. Similar to the SF-36, the SF-12 also produces scores for eight individual domains, with composite physical and mental component scores. All scales of the SF-12 are calculated to use the same standardized norm, with a mean (standard deviation [SD]) of 50 (10). For the current analysis, only physical and mental component scores were analyzed. The SQLS–R4 is a validated 33-item self-report measure from which two domains of quality-of-life are scored: "psychosocial feelings" and "cognition/vitality" [24]. Items are scored on a 5-point Likert scale from never to always. Both individual domain and total scores are standardized by a scoring algorithm to a scale from 0 to 100.

Safety and tolerability were assessed by recording the occurrence of treatment-emergent AEs (TEAEs) at each visit. Vital signs were recorded at screening, baseline, treatment months 3 and 6, and then every 6 months. Weight was evaluated at baseline and every 6 months. Urinalysis and serum tests of hematology, chemistries, and prolactin were obtained at screening and every 12 months. The occurrence of extrapyramidal symptoms was evaluated using the extrapyramidal symptom rating scale (ESRS) [25] at baseline and treatment Months 3, 6, 12, 18, and 24.

Data analysis

Sample size determination was based on estimated 1-year rates of relapse of 30% for RLAI and 42% for quetiapine, as observed in a previous relapse study that reported 1-year relapse in 27% treated with long-acting depot antipsychotic versus 42% with oral medication [14]. A total of 251 patients was needed for each treatment arm to detect a difference in relapse rates with a power of 80% and a two-tailed significance level of 5%. To adjust for patient discontinuations for reasons other than disease relapse, estimated at 20%, a minimum total of 628 patients was planned for treatment with RLAI and quetiapine. As a consequence, approximately 63 patients were expected to enter the trial for treatment with aripiprazole.

A preplanned analysis was performed after the last patient had completed 1 year of treatment. The study was to be stopped if the last patient completed 1 year of follow-up and a difference in time-to-relapse at the 0.1% significance level (two-tailed) was observed.

This study used an intent-to-treat analysis for both efficacy and tolerability measures, with all patients treated with at least a single dose of study drug eligible for analyses. Patients who dropped out before receiving the first dose of study drug were analyzed separately. Endpoint was defined as the final assessment for patients completing the full 2-year treatment or the last observation carried forward.

Time-to-relapse, the primary efficacy measure, was evaluated using the Kaplan–Meier method. The mean time-to-relapse was estimated by means of the Kaplan–Meier

product limit method. In this estimation, nonrelapsed drop outs are accounted for by decreasing the number of patients considered to be at risk at the time of the relapse event following the drop out. As this method does not use the actual observation time for drop outs, the Kaplan–Meier estimate of the time-to-relapse differs from the mean observed time of the patients and, if there are many drop outs, it can be higher than the mean treatment duration.

Demographics, disease characteristics, and TEAEs were assessed using descriptive analyses. Within-group differences for ordinal/continuous data were assessed using the Wilcoxon two-sample test. Nominal data were tested using the Fischer exact test. All statistical tests were interpreted at the 5% significance level (two-tailed). Due to the small sample size for aripiprazole, between-group comparisons were descriptive only. Because aripiprazole was available at a limited number of centers, a subanalysis was performed to include an evaluation of patients treated with either RLAI or quetiapine only at those facilities that enrolled patients for aripiprazole.

Results

The results of the prespecified analysis after the last patient had completed 1 year of treatment led to the recommendation by independent experts to terminate the trial early due to achieving the predetermined difference in the primary endpoint. Twenty-six patients (19 RLAI and 7 aripiprazole; 5%) were ongoing at the time of termination.

Patients

A total of 401 patients were randomized (355 to RLAI and 46 to aripiprazole). The data collected on 12 patients from one site (all treated with RLAI) were excluded through a decision made by the quality assurance department because the study at that site was not conducted in a manner consistent with Good Practice Guidelines. An additional 15 patients (14 RLAI and 1 aripiprazole) did not receive trial medication, leaving an evaluable sample of 374 patients (329 RLAI and 45 aripiprazole).

Baseline demographics for each treatment group are shown in Table 1. According to CGI–S, the percentage of patients at least "moderately ill" at baseline was 62.3% with RLAI and 61.4% with aripiprazole. Baseline measures of comorbidity were comparable among treatment groups. During the study, concomitant medications were used by 82.7% of patients treated with RLAI and 84.4% with aripiprazole, most commonly psycholeptics, anti-Parkinson drugs, anti-epileptics, and analgesics.

Treatment was completed by 151 RLAI patients (45.9%) and 9 aripiprazole patients (20.0%). Withdrawal for reasons other than relapse occurred in 105 RLAI patients (31.9%) and 17 aripiprazole patients (37.8%). The most commonly reported reason for dropping out, other than relapse, was withdrawal of consent (59 of the 178 noncompleters with RLAI [33.1%] and 9 of the 36 noncompleters with aripiprazole [25.0%]). AEs resulted in

Table 1 Baseline characteristics

Characteristic	RLAI ($n = 329$)	Aripiprazole ($n = 45$)
Age, years, mean (SD)	40.6 (12.5)	40.9 (12.9)
Gender, *n* (%)		
Male	195 (59.3)	25 (55.6)
Female	134 (40.7)	20 (44.4)
Race, *n* (%)		
Caucasian	320 (97.3)	44 (97.8)
Other	9 (2.7)	1 (2.2)
Diagnosis, *n* (%)		
Schizophrenia	273 (83.0)	37 (82.2)
Schizoaffective disorder	56 (17.0)	8 (17.8)
Time since symptom diagnosis, years, mean (SD)	9.9 (9.9)	8.1 (9.8)
Number of psychiatric hospitalizations, mean (SD)	5.0 (6.5)	5.8 (5.3)
Previous antipsychotic, *n* (%)		
Risperidone	164 (49.8)	22 (48.9)
Olanzapine	68 (20.7)	12 (26.7)
Conventional oral	97 (29.5)	11 (24.4)
Reason for changing antipsychotic, *n* (%)[a]		
Insufficient efficacy on negative symptoms	96 (29.2)	9 (20.0)
Insufficient efficacy on positive symptoms	42 (12.8)	7 (15.6)
Insufficient efficacy on general symptoms	64 (19.5)	7 (15.6)
Side effects	57 (17.3)	21 (46.7)
Patient request	85 (25.8)	9 (20.0)
Compliance	51 (15.5)	2 (4.4)
Other	4 (1.2)	0
Symptom severity, mean score (SD)		
PANSS	72.7 (21.0)	76.1 (25.0)
CGI–S	2.8 (1.0)	2.8 (1.0)
MADRS	12.7 (7.6)	13.3 (7.1)
SOFAS	55.6 (13.1)	55.8 (16.5)
ESRS	4.2 (6.7)	5.7 (9.2)
SQLS–R4	39.56 (17.12)	46.15 (17.45)

CGI–S Clinical global impression–severity, *ESRS* Extrapyramidal symptom rating scale, *MADRS* Montgomery–Asberg depression rating scale, *PANSS* Positive and negative syndrome scale, *RLAI* risperidone long-acting injectable, *SD* standard deviation, *SOFAS* Social and occupational functioning assessment scale, *SQLS–R4* Schizophrenia quality-of-life scale–revision 4

[a] More than one reason permitted for each patient

Table 2 Criteria for relapse among those patients who relapsed

Reason	RLAI ($n = 54$) n (%)[a]	Aripiprazole ($n = 12$) n (%)[a]
Clinical deterioration	41 (75.9)	8 (66.7)
Increased care and ≥25% increase in PANSS	33 (61.1)	7 (58.3)
Psychiatric hospitalization	33 (61.1)	2 (16.7)
Requiring a dose higher than the registered dose	10 (18.5)	1 (8.3)
Suicidal/homicidal ideation	8 (14.8)	0
Violent behavior	6 (11.1)	1 (8.3)
Self-injury	5 (9.3)	0

PANSS Positive and negative syndrome scale, *RLAI* risperidone long-acting injectable

[a] More than one reason permitted for each patient

withdrawal for 7 patients with RLAI (3.9%) and 1 with aripiprazole (2.8%). Insufficient efficacy resulted in withdrawal for 4 patients with RLAI (2.2%) and none with aripiprazole. In addition, 19 patients treated with RLAI and 7 with aripiprazole were ongoing at the time the study was stopped per the prespecified analysis by the sponsor.

Mean (SD) endpoint study drug dosage was 35.6 (10.4) mg every 2 weeks with RLAI and 15.1 (6.6) mg daily with aripiprazole. Mean (SD) duration of treatment was 483.8 (277.8) days with RLAI and 373.2 (271.6) days with aripiprazole.

Efficacy

Efficacy analyses were performed for 327 patients with RLAI and 44 with aripiprazole. No follow-up efficacy data were available for the other 2 RLAI and 1 aripiprazole patients.

Relapse

Relapse occurred in 54 patients treated with RLAI (16.5%; 95% CI: 12.7–21.0%) and 12 patients with aripiprazole (27.3%; 95% CI: 15.0–42.8%). The Kaplan–Meier estimate of mean (standard error [SE]) relapse-free period was 607.1 (11.4) days with RLAI and 313.7 (20.4) days with aripiprazole. The lower confidence limit for the 1st quartile of the relapse-free period was 691 days with RLAI and 111 days with aripiprazole. Criteria met that resulted in a diagnosis of relapse are shown in Table 2. A Kaplan–Meier plot was generated for time to confirmed relapse (Fig. 1). Estimated mean (SD) time-to-relapse among patients experiencing a relapse was 244.9 (208.0; 95% CI: 188.1–301.7) days with RLAI and 147.7 (116.3; 95% CI: 73.8–221.6) days with aripiprazole.

Remission

Remission was achieved at some point during the study in 167 patients treated with RLAI (51.1%; 95% CI: 45.5–56.6%) and 15 (34.1%; 95% CI: 20.5–49.9%)

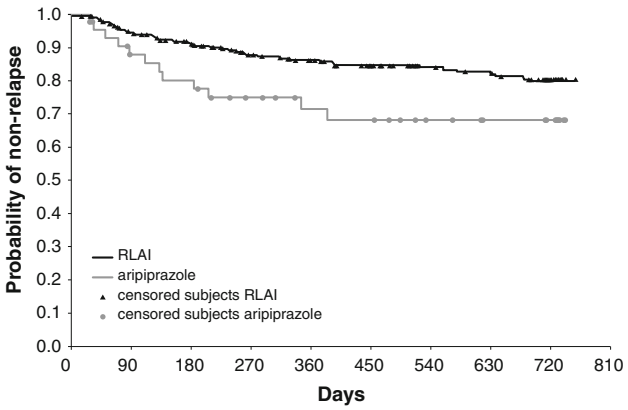

Fig. 1 Kaplan–Meier curve of time-to-relapse. Among 329 patients treated with RLAI, relapse occurred in 54 patients (16.5%); and among 45 patients treated with aripiprazole, relapse occurred in 12 patients (27.3%). *RLAI* Risperidone long-acting injectable

aripiprazole patients. The Kaplan–Meier estimate of mean (SE) time-to-remission was 422.6 (14.3) days with RLAI and 378.4 (27.2) days with aripiprazole. The first quartile of the time-to-remission was 251 (95% CI: 183–266) days with RLAI and 267 (95% CI: 183–344) days with aripiprazole. The upper confidence limit of the median time-to-remission could not be computed for aripiprazole because <50% reached remission in this arm. Remission was maintained until the end of the trial for 144 (44.0%; 95% CI: 38.6–49.6%) RLAI patients and 13 (29.6%; 95% CI: 16.8–45.2%) aripiprazole patients. Mean (SD) time in remission was 540.8 (181.4; 95% CI: 513.1–568.5) days with RLAI and 559.9 (157.2; 95% CI: 472.8–646.9) days with aripiprazole.

Other efficacy outcomes

Endpoint changes in PANSS total and subscale scores, PANSS factor scores based on Marder, MADRS, and CGI are shown in Table 3. Significant within-treatment changes were noticed for many variables with both treatments. Although numerical differences often seemed to favor RLAI, there was no statistical evidence because confidence

Table 3 Endpoint changes versus baseline in secondary efficacy outcomes

Efficacy measure	RLAI ($n = 326$)		Aripiprazole ($n = 44$)	
	Mean change ± SD (95% CI)	*P* values vs. baseline	Mean change ± SD (95% CI)	*P* values vs. baseline
PANSS				
Total	−9.33 ± 25.65 (−12.12 to −6.53)	<0.0001	−7.66 ± 27.99 (−16.17 to 0.85)	0.0873
General	−4.63 ± 13.18 (−6.07 to −3.20)	<0.0001	−3.86 ± 13.86 (−8.08 to 0.35)	0.0776
Positive	−0.97 ± 7.90 (−1.83 to −0.11)	<0.0001	0.77 ± 7.65 (−1.55 to 3.10)	0.8734
Negative	−3.73 ± 7.09 (−4.50 to −2.96)	<0.0001	−4.57 ± 8.92 (−7.28 to −1.86)	0.0020
PANSS factor scores, based on Marder				
Negative	−3.90 ± 6.58 (−4.61 to −3.18)	<0.0001	−4.68 ± 8.47 (−7.26 to −2.11)	0.0005
Positive	−1.97 ± 8.33 (−2.88 to −1.06)	<0.0001	−0.68 ± 8.51 (−3.27 to 1.91)	0.3875
Disorganized thought	−2.25 ± 6.09 (−2.91 to −1.59)	<0.0001	−2.61 ± 6.27 (−4.52 to −0.71)	0.0197
Uncontrolled hostility/excitement	0.08 ± 4.34 (−0.39 to 0.56)	0.1069	1.20 ± 4.88 (−0.28 to 2.69)	0.2457
Anxiety/depression	−1.30 ± 4.31 (−1.77 to −0.83)	<0.0001	−0.89 ± 4.12 (−2.14 to 0.36)	0.1301
MADRS scores				
Total	−2.85 ± 8.65 (−3.79 to −1.91)	<0.0001	−2.64 ± 10.16 (−5.73 to 0.45)	0.0995
Apparent sadness	−0.51 ± 1.31 (−0.65 to −0.36)	<0.0001	−0.48 ± 1.76 (−1.01 to 0.06)	0.0830
Reported sadness	−0.37 ± 1.36 (−0.52 to −0.22)	<0.0001	−0.57 ± 1.74 (−1.10 to −0.04)	0.0255
CGI				
Severity	−0.33 ± 1.25 (−0.46 to −0.19)	<0.0001	−0.11 ± 1.32 (−0.51 to 0.29)	0.6238
Change	0.03 ± 1.23 (−0.10 to 0.17)	NR	−0.55 ± 1.25 (−0.92 to −0.17)	NR

CGI clinical global impression, *CI* confidence interval, *MADRS* Montgomery–Asberg depression rating scale, *NR* not reported, *PANSS* positive and negative syndrome scale, *RLAI* risperidone long-acting injectable, *SD* standard deviation

Improvements are noted by decreases in values for all scores, except for CGI–Change. CGI–Change ranges from 3 = very much improved to −3 = very much worse; therefore, an increase in CGI–Change denotes improvement

intervals within the aripiprazole treatment arm were quite wide and overlapping with the confidence intervals for RLAI. According to CGI–S at baseline, 62.3% (95% CI: 56.8–67.6%) of RLAI and 61.4% (95% CI: 45.5–75.6%) of aripiprazole patients were considered to be "moderately ill" or worse; this fell to 45.2% (95% CI: 39.7–50.8%) and 59.1% (95% CI: 43.3–73.7%), respectively, at endpoint. Among patients treated with RLAI versus aripiprazole, endpoint CGI–C was "much improved" or "very much improved" in 11.3% (95% CI: 8.1–15.3%) versus 4.6% (95% CI: 0.6–15.5%) of patients, respectively; "minimally improved" in 15.0% (95% CI: 11.3–19.4%) versus 11.4% (95% CI: 3.8–24.6%); "unchanged" in 51.5% (95% CI: 46.0–57.1%) versus 40.9% (95% CI: 26.3–56.8%); "minimally worse" in 9.8% (95% CI: 6.8–13.6%) versus 18.2% (95% CI: 8.2–32.7%); and "much worse" or "very much worse" in 12.3% (95% CI: 8.9–16.3%) versus 25.0% (95% CI: 13.2–40.3%).

Functioning and quality-of-life

SOFAS scores increased throughout treatment with RLAI, indicating gradual improvement that was significant from the first post-baseline assessment at month 6 onwards. With aripiprazole, SOFAS scores improved from baseline to month 18 and remained unchanged thereafter. Statistically significant improvements versus baseline were found at 18 and 24 months ($P \leq 0.004$). At endpoint, mean (SD) changes versus baseline in SOFAS were 6.63 (15.20; 95% CI: 4.90–8.36) with RLAI ($P < 0.0001$) and 3.24 (20.29; 95% CI: −3.43 to 9.90) with aripiprazole (not significant; $P = 0.5873$).

SF-12 physical and mental component scores increased from baseline to month 24 for RLAI-treated patients ($P < 0.0001$), indicating improved quality-of-life. Physical component scores did not change significantly from baseline with aripiprazole; however, significant changes were seen with aripiprazole for the mental component score from baseline at months 1, 3, 6, 18, and endpoint ($P < 0.05$). Mean (SD) baseline to endpoint changes in SF-12 physical and mental component scores were 2.09 (9.04; 95% CI: 1.05–3.12) and 3.15 (10.43; 95% CI: 1.96–4.35), respectively for RLAI (both $P < 0.0001$); and 2.38 (10.36; 95% CI: −0.85 to 5.61) (not significant) and 4.93 (12.10; 95% CI: 1.16–8.69) ($P = 0.005$), respectively, for aripiprazole.

SQLS–R4 total scores decreased gradually from baseline in both treatment groups, representing improved quality-of-life. Significant changes were seen starting at the first post-baseline assessment at 1 month onwards for each treatment group. Mean (SD) baseline to endpoint changes in SQLS–R4 for RLAI versus aripiprazole were: total −5.70 (14.76) versus −10.86 (17.96); psychosocial −5.60 (16.39) versus −11.24 (18.10); and vitality −5.85 (15.58) versus −10.28 (20.99). Each of these changes was significant for RLAI ($P < 0.0001$) and aripiprazole ($P < 0.01$).

Subanalysis of RLAI and quetiapine patients from sites enrolling aripiprazole patients

At sites enrolling patients for aripiprazole, 46 patients were randomized to RLAI and 52 to quetiapine. Demographics of this subset were generally similar to those for the entire RLAI group, with differences described below. Age was similar between the aripiprazole group and the entire RLAI sample; however, mean age was higher among the RLAI and quetiapine subset enrolled at the aripiprazole sites (46.9 ± 14.6 years). Likewise, time since first onset of psychotic symptoms was longer in the RLAI and quetiapine subset (17.8 ± 14.0 years with RLAI and 18.7 ± 12.4 years with quetiapine) compared with the entire RLAI sample (13.8 ± 11.1 years), the entire quetiapine sample (14.1 ± 11.4), and the aripiprazole population (14.1 ± 11.5). Time since first antipsychotic treatment was also longer in the RLAI and quetiapine subset enrolled at the aripiprazole sites (16.0 ± 14.0 years with RLAI and 15.6 ± 10.3 years with quetiapine) compared with the entire sample (12.5 ± 10.9 years with RLAI and 12.7 ± 10.7 years with quetiapine) and aripiprazole (12.2 ± 10.7 years). The subset of RLAI and quetiapine enrolled at aripiprazole sites were mainly diagnosed with paranoid schizophrenia (56.0%), with 16.7% diagnosed with undifferentiated schizophrenia, 16.7% with residual schizophrenia, and 10.7% with disorganized schizophrenia. Reasons for switching in the subset including insufficient efficacy for negative symptoms (69.4%), positive symptoms (18.4%), and general symptoms (31.6%), as well as side effects for 15.3%, patient request (13.3%), and patient compliance (9.2%).

Among efficacy outcome measures, differences when using the subset compared with the entire RLAI population were noted for the primary parameter of number of relapses and endpoint change in PANSS total score. Within the subset, relapses occurred for 3 patients (6.5%) treated with RLAI and 12 patients (24.0%) with quetiapine. Using the full sample enrolled in this trial, relapse occurred for 16.5% treated with RLAI and 31.3% with quetiapine [16]. The log-rank test showed a significant difference in relapse between patients treated with RLAI versus quetiapine in the subset of patients enrolled at aripiprazole sites only ($P = 0.0219$). Criteria met that resulted in a diagnosis of relapse were comparable among patients in the entire RLAI and quetiapine sample, the subset enrolled at aripiprazole sites, and patients treated with aripiprazole.

Mean PANSS total scores in the subset of patients treated at aripiprazole sites at baseline and endpoint, respectively, were 86.5 ± 21.4 and 68.4 ± 28.5 for RLAI patients and 88.0 ± 25.2 and 79.4 ± 30.3 with quetiapine. Mean PANSS total scores for the entire sample at baseline and endpoint, respectively, were 72.7 ± 21.1 and 63.4 ± 24.8 with RLAI and 73.2 ± 22.2 and 72.1 ± 27.0 with quetiapine.

Safety and tolerability

Safety data were available for 329 RLAI and 45 aripiprazole patients. TEAEs occurred similarly between treatment groups (Table 4). The most common TEAEs were psychiatric symptoms (43.2% of patients with RLAI and 53.3% with aripiprazole), gastrointestinal disorders (6.1% RLAI and 22.2% aripiprazole), weight gain (7.0% RLAI and 4.4% aripiprazole), headache (6.1% RLAI and 11.1% aripiprazole), and potentially prolactin-related TEAEs (4.6% RLAI and 0 aripiprazole). Based on the number of TEAEs, recovery from TEAEs had occurred at endpoint for 75.6% of TEAEs occurring while treated with RLAI and 86.9% with aripiprazole. Serious TEAEs were reported by 19.1% of patients with RLAI and 15.6% with aripiprazole.

Table 4 Treatment-emergent adverse events (TEAEs)

	RLAI ($n = 329$)	Aripiprazole ($n = 45$)
Total number of TEAEs reported	692	130
Patients with any TEAE, *n* (%)	225 (68.4)	31 (68.9)
Patients with serious TEAE, *n* (%)	63 (19.1)	7 (15.6)
Severity, *n* (%)		
Mild	371 (53.6)	67 (51.5)
Moderate	262 (37.9)	52 (40.0)
Severe	59 (8.5)	11 (8.5)
Action taken regarding study treatment, *n* (%)		
No treatment change	521 (75.3)	93 (71.5)
Dosage adjustment	103 (14.9)	29 (22.3)
Treatment discontinuation	68 (9.8)	8 (6.2)
Relationship to study treatment, *n* (%)		
None	349 (50.4)	57 (43.8)
Doubtful	153 (22.1)	16 (12.3)
Possible	102 (14.7)	40 (30.8)
Probable	51 (7.4)	13 (10.0)
Very likely	37 (5.3)	4 (3.1)

RLAI Risperidone long-acting injectable

The most common serious TEAEs were psychiatric. The most frequently reported individual serious psychiatric TEAEs with RLAI were schizophrenia ($n = 14$) and psychotic disorder ($n = 8$). There were four serious psychiatric TEAEs with aripiprazole; two psychotic disorder and one each of delirium and delusion. Death occurred in 3 patients treated with RLAI (2 patients committed suicide and 1 had deep-vein thrombosis and peptic ulcer perforation) and none with aripiprazole. None of the deaths were considered to be potentially or probably related to study drug by the primary investigator.

Changes in vital signs, urinalysis, and serum hematology and chemistry tests for each treatment group were small, with no clinically significant differences. Weight increase was reported as an AE by 7.0% of patients with RLAI and 4.4% with aripiprazole. Mean (SD) weight and body mass index increased slightly from baseline to 24 months among patients treated with RLAI (1.2 [7.1] kg and 0.39 [2.38] kg/m^2, respectively), and decreased slightly among those treated with aripiprazole (−1.5 [5.7] kg and −0.46 [1.85] kg/m^2, respectively).

Treatment-emergent potentially prolactin-related AEs were reported in 15 patients with RLAI (4.6%). Hyperprolactinemia, based on laboratory testing, occurred in 43 patients with RLAI (13.1%). There were no reports of potentially prolactin-related TEAEs with aripiprazole.

Extrapyramidal TEAEs were reported for 10.3% of patients treated with RLAI and 4.4% with aripiprazole, most commonly Parkinsonism, hyperkinesias, and tremor. Changes in total ESRS scores throughout treatment are shown in Fig. 2. Mean (SD) baseline to endpoint changes in total ESRS were −2.32 (4.56) with RLAI ($P < 0.0001$) and −3.24 (9.05) with aripiprazole ($P = 0.02$). Within-treatment improvements in ESRS compared with baseline were significant at each assessment and endpoint for RLAI ($P < 0.001$) and at endpoint and each assessment (except for month 24) for aripiprazole ($P < 0.05$).

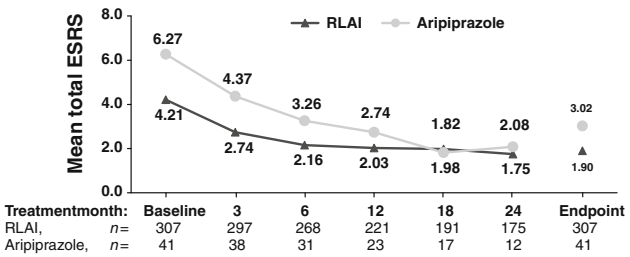

Fig. 2 Changes in ESRS scores. Within-treatment improvements were significantly compared with baseline at each assessment and endpoint for RLAI ($P < 0.001$), and at endpoint and each assessment (except for month 24) for aripiprazole ($P < 0.05$). *ESRS* Extrapyramidal symptom rating scale; *RLAI* Risperidone long-acting injectable

Discussion

In this study of patients with clinically stable schizophrenia or schizoaffective disorder, risk of relapse was numerically lower with RLAI (16.5%) compared with aripiprazole (27.3%). There was no statistically significant difference shown since the 95% confidence interval for the comparatively small sample of aripiprazole patients was quite wide (15.0–42.8%). These data are similar to relapse data reported for stable patients switched to RLAI with a 1-year relapse rate of 18% [26]. Earlier studies with aripiprazole have reported relapse in 20 and 57% of patients during 6-month follow-up [27, 28]. Mean relapse-free periods in stable patients with schizophrenia or schizoaffective disorder after a treatment change was 607 days with RLAI and 314 days with aripiprazole. The most common criteria that resulted in a diagnosis of relapse were similar for both RLAI and aripiprazole in the current study, including clinical deterioration, increased care, and a 25% increase in PANSS.

Remission was achieved during the study for 51.1% of patients treated with RLAI and 34.1% treated with aripiprazole. Mean time-to-remission was 423 days with RLAI and 378 days with aripiprazole. Once remission was achieved, most patients treated with either RLAI or aripiprazole maintained remission. Improvements in psychotic symptoms favored RLAI for changes in PANSS scores, with similar improvements between treatments seen in depressive symptoms. Significant changes from baseline occurred with RLAI for PANSS total scores, Marder factors, response rate and remission, CGI–S, and MADRS. Aripiprazole resulted in significant improvements in PANSS negative symptoms and MADRS reported sadness. Overall improvement, as rated by the CGI–C, occurred for 26% of patients treated with RLAI, with 52% unchanged and 22% worse. With aripiprazole, 16% were improved, 41% unchanged, and 43% worse. Patients treated with RLAI experienced improved functioning and quality-of-life over 24 months with significant changes from baseline in SOFAS, SF-12, and SQLS–R4. Significant changes from baseline were seen with aripiprazole for the SF-12 mental component score and SQLS–R4.

A subanalysis of only those patients treated at sites enrolling aripiprazole patients showed a few demographic differences, including older age and longer time since initial diagnosis and first antipsychotic treatment among the RLAI and quetiapine patients enrolled at aripiprazole sites only. Furthermore, baseline PANSS total scores were higher for both RLAI and quetiapine patients treated at only the aripiprazole sites; however, endpoint values were comparable. Therefore, despite difference in baseline characteristics, there seemed to be no changes in treatment effect between the subset and entire sample analyses,

supporting the statistical conclusions for the primary parameter and PANSS total scores reached when using the full study sample.

Tolerability was generally good with RLAI and aripiprazole in the current study, and comparable to earlier reports [18, 26, 28], with no new safety issues identified. Most TEAEs were mild or moderate in severity and did not result in a change in therapy. Weight gain affected <10% of patients treated with RLAI or aripiprazole, with a mean change of 1.2 kg with RLAI and −1.5 kg with aripiprazole. Extrapyramidal and potentially prolactin-related TEAEs occurred more often with RLAI, while gastrointestinal TEAEs occurred more frequently with aripiprazole. Interestingly, the most common reason at baseline for changing antipsychotic for patients switching to aripiprazole was medication side effects (47%), while side effects were listed as a reason for changing therapy for only 17% switched to RLAI. Despite higher baseline medication intolerability reported among patients switching to aripiprazole, aripiprazole was generally well tolerated in this study, with only 6% discontinuing aripiprazole due to adverse events.

Limitations of the ConstaTRE design have been previously detailed [16].The current analysis is further limited as ConstaTRE was not powered for the aripiprazole arm. Due to relatively few patients treated with aripiprazole in this study, conclusions comparing treatment with RLAI versus aripiprazole are limited and reported comparisons should be interpreted cautiously. Interpretation of data from this study is additionally limited by those factors inherent to open-label treatment studies and a comparison of an injectable versus oral therapy. Previous work has shown comparable efficacy for patients with stable schizophrenia treated with RLAI versus oral risperidone, although tolerability was better with RLAI [29]. In addition, evaluation of randomized trial data suggests that the efficacy of risperidone is better than with quetiapine [30] and similar to aripiprazole [31]. Further studies may wish to specifically evaluate relapse and remission between these oral risperidone and RLAI to determine if the differences seen in the current study reflect an advantage of injectable therapy or an advantage for risperidone. Furthermore, 2-year treatment was not completed due to relapse or other reasons for half of the evaluable sample. Rates and reasons for withdrawal were similar between assigned treatments in the current study and were also comparable to an early, analogous study of stable patients with schizophrenia or schizoaffective disorder randomized to oral risperidone or haloperidol [18]. In that study, 18% with either risperidone or haloperidol patients withdrew due to patient choice, and 12% with risperidone and 15% with haloperidol withdrew due to side effects. Withdrawal for reasons other than relapse occurred in 14% of patients with risperidone and 20% with haloperidol. Similarly, 54% of stable, schizophrenic patients randomized to aripiprazole discontinued treatment during a 6-month follow-up, with 69% withdrawing due to lack of efficacy or AEs, and 21% withdrawing consent [28]. Finally, face-to-face time between patient and staff was greater among patients treated with RLAI, due to appointments required for injection administration rather than phone follow-up for patients using aripiprazole. Therapeutic benefit with RLAI may have been accentuated by more frequent face-to-face contacts.

Conclusions

Despite limitations in interpretations due to the small sample size of aripiprazole, data from the current study support earlier studies demonstrating good relapse prevention in stable patients with schizophrenia or schizoaffective disorder treated with RLAI. In the current study, relapse was numerically less frequent among patients using RLAI compared with the oral atypical antipsychotic aripiprazole, although this difference was not statistically significant. General improvement and functional recovery were also better with RLAI. Tolerability was generally good and similar with both drugs.

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