A. Ciudad[1]
E. Álvarez[2]
M. Bousoño[3]
J. M. Olivares[4]
J. C. Gómez[1]

Safety and tolerability of olanzapine versus risperidone: a one-year randomized study in outpatients with schizophrenia with prominent negative symptoms

[1] Lilly Research Laboratories
Madrid (Spain)
[2] Hospital de la Santa Creu i Sant Pau. UAB
Barcelona (Spain)
[3] Facultad de Medicina
Universidad de Oviedo
Oviedo (Spain)
[4] Complejo Hospitalario Xeral-Cíes
Vigo (Spain)

Objective. To evaluate the safety and tolerability of long-term treatment with olanzapine versus risperidone in schizophrenic outpatients with prominent negative symptoms.

Methods. This was a multi-center, randomised, open-label, parallel, dose-flexible, 1 year study of outpatients with schizophrenia (DSM-IV criteria) with prominent negative symptoms (SANS Global score ≥ 10). Safety was evaluated by recording treatment-emergent adverse events, vital signs, body weight and, when available, laboratory parameters. Extrapyramidal symptoms (EPS) were evaluated by a questionnaire based on the UKU scale, and sexual dysfunction by the Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ).

Results. The mean (± SD) modal dose throughout the study was 12.3 (± 6.3) mg/day for olanzapine and 5.2 (± 2.5) mg/day for risperidone. EPS were significantly more frequent in the risperidone-treated patients 50.4 % versus 28.9 % for olanzapine (p = 0.0006). Olanzapine patients showed significantly greater reductions (improvement) from baseline in the PRSexDQ score (p = 0.0292) and risperidone patients reported significantly more sexual adverse events (21.1 % versus 7.3 % for olanzapine; p = 0.0018). Mean body weight gain was not significantly different at endpoint (3.5 kg gained with olanzapine versus 1.9 kg gained with risperidone; p = 0.3522), but the proportion of patients showing a body weight increase ≥ 7% was higher among the olanzapine-treated patients (37.8 % versus 16.8 %; p = 0.0012).

Conclusions. Significantly less treatment-emergent extrapyramidal and sexual adverse events were observed in patients treated with olanzapine compared to those treated with risperidone. Mean body weight increases with both drugs were not significantly different after one year. Olanzapine patients presented a significantly higher incidence of clinically important body weight increase when compared with patients treated with risperidone.

Key words:
Olanzapine. Risperidone. Schizophrenia. Tolerability. Safety.

Actas Esp Psiquiatr 2007;35(2):105-114

Seguridad y tolerabilidad de olanzapina y risperidona: un estudio aleatorizado de 1 año de duración en pacientes con esquizofrenia y sintomatología negativa prominente tratados de manera ambulatoria

Objetivo. Evaluar la seguridad y tolerabilidad de olanzapina y risperidona en el tratamiento a largo plazo de pacientes esquizofrénicos con sintomatología negativa prominente tratados de manera ambulatoria.

Métodos. Un ensayo clínico multicéntrico, aleatorizado, efectuado con diseño abierto y grupos paralelos, con administración de dosis flexibles, de 1 año de duración, en pacientes con esquizofrenia (criterios DSM-IV) con sintomatología negativa prominente (puntuación global en la escala SANS ≥ 10). La seguridad se evaluó mediante la determinación de los efectos adversos asociados al tratamiento, los signos vitales, el peso corporal y, siempre que fue posible, diversos parámetros analíticos. Los síntomas extrapiramidales (SEP) fueron evaluados mediante un cuestionario fundamentado en la escala UKU, mientras que la disfunción sexual lo fue a través del cuestionario de disfunción sexual relacionada con medicamentos psicotrópicos (PRSexDQ).

Resultados. La dosis modal media (± DE) a lo largo del estudio fue de 12,3 (± 6,3) mg/día respecto a olanzapina y de 5,2 (± 2,5) mg/día respecto a risperidona. Los SEP fueron significativamente más frecuentes en los pa-

Correspondence:
Antonio Ciudad Herrera
Lilly Research Laboratories
Av. de la Industria, 30
28108 Alcobendas (Madrid) (Spain)
E-mail: ciudad_antonio@Lilly.com

cientes tratados con risperidona que en los que recibieron olanzapina (50,4 y 28,9 %, respectivamente; p=0,0006). Los pacientes del grupo de olanzapina mostraron reducciones (mejoría) significativamente mayores (respecto a los valores existentes al inicio del estudio) en la puntuación del PRSexDQ (p=0,0292), mientras que los del grupo de risperidona presentaron una incidencia significativamente mayor de efectos adversos de carácter sexual (21,1% en los pacientes tratados con risperidona y 7,3% en los pacientes tratados con olanzapina; p = 0,0018). El incremento medio del peso corporal no fue significativamente diferente entre ambos fármacos al final del estudio (3,5 y 1,9 kg en los grupos de olanzapina y risperidona, respectivamente; p = 0,3522), pero la proporción de pacientes que mostraron un incremento del peso corporal ≥7% fue superior en el grupo de olanzapina (37,8 y 16,8%, respectivamente; p=0,0012).

Conclusiones. En comparación con los pacientes tratados con risperidona, los que recibieron olanzapina presentaron una incidencia significativamente menor de síntomas extrapiramidales asociados al tratamiento y de efectos adversos de carácter sexual. Los incrementos medios del peso corporal observados con ambos fármacos no fueron significativamente diferentes entre sí tras 1 año de tratamiento. En comparación con los pacientes del grupo de risperidona, los pacientes tratados con olanzapina presentaron una incidencia significativamente mayor de aumento clínicamente importante del peso corporal.

Palabras clave:
Olanzapina. Risperidona. Esquizofrenia. Tolerabilidad. Seguridad.

INTRODUCTION

Schizophrenia is a disease of low prevalence, but frequently characterized by a chronic recurrent course[1]. Introduction of conventional antipsychotics implied great progress in the treatment of schizophrenia, but at least 30% of schizophrenic patients may exhibit an inadequate or poor response to conventional (typical) antipsycotics[2,3] and as many as 60% experience relapse after 1 year of therapy[1]. A substantial proportion of patients may also be non-compliant with their medication, contributing to a pattern of repeated hospital admissions and progressive social and occupational dysfunction. The estimated rate of non-compliance is between 11% and 80%[4] and a common reason for non-compliance is the occurrence of adverse events, particularly treatment-emergent extrapyramidal symptoms (EPS)[5]. These therapeutic limitations made necessary the availability of more effective and better tolerated drugs.

The focus of new drug development for the treatment of schizophrenia has been to obtain compounds with a broader efficacy profile, targeting negative, cognitive and affective symptoms; and less likelihood to provoke treatment-emergent EPS and other perturbating adverse events[5,6]. The resulting second-generation atypical antipsychotics have been extensively investigated in randomized double-blind clinical trials comparing them with haloperidol that have demonstrated clear advantages in terms of both alleviating symptoms and fewer adverse effects. Nevertheless, there are limited data on their relative qualities in specific domains and safety in relevant populations[7].

Risperidone and olanzapine separately have demonstrated good tolerability and efficacy in the treatment of psychotic disorders[8-14]. Although they share greater 5-HT_{2A} than D_2 antagonism, they differ in their profile of receptor binding affinities[15], providing for *in vivo* different features. Four head-to-head prospective studies have compared these two agents[15-18], reporting that both antipsychotics significantly reduced positive and negative symptoms of schizophrenia. Yet, there were greater effects in alleviating positive and affective symptoms with risperidone and negative symptoms and response rates with olanzapine. At the time, an increased incidence of treatment-emergent EPS was reported in patients treated with risperidone, and an increased incidence of weight gain was reported in patients treated with olanzapine. The results of such clinical trials have been confirmed by studies performed under naturalistic conditions in a large number of outpatients[19] and hospitalized schizophrenic patients[20]. However, none of these studies has compared both antipsychotics in patients with predominantly negative symptoms, a relevant subset of subjects with poor prognosis for whom the confirmation of the improved outcome is essential to establish the relevance for the clinical practice of novel antipsychotics.

The benefits provided by the use of new antispsychotics for the treatment of schizophrenia should be evaluated within the context of daily clinical practice in patients receiving these drugs under naturalistic conditions. But the main limitation of observational naturalistic studies is their non-randomized nature. Randomized allocation followed by an open label flexible-dose follow-up provides scientific rigorousness (internal validity) on the one hand, and ability to generalization of results (external validity) on the other.

This article reports the results of an open-label, flexible-dose, randomized, long-term study comparing the safety and tolerability as well as some efficacy results of olanzapine and risperidone in the routine clinical practice in outpatients with DSM-IV diagnosis of schizophrenia with predominantly negative symptoms previously treated with conventional antipsychotics.

METHODS

Study design

This was a multicenter, randomized, open-label, flexible-dose, parallel-group comparison of olanzapine and risperidone performed in 21 outpatient psychiatric settings in Spain from January 2001 to May 2003. Each center's ethics committee approved the study and informed consent was obtained from all eligible subjects after the procedures and potential adverse events were fully explained. The study was conducted according to the Declaration of Helsinki guidelines. Randomized allocation to risperidone or olanzapine took place at the first visit and there was not any washout period for previous antipsychotic and/or anticholinergic medications, although overlapping during the first month was allowed.

Patient population

Participants in the study were outpatients aged 18 to 65 years old with a DSM-IV diagnosis of schizophrenia, and a baseline global score in the Scale for the Assessment of Negative Symptoms[21] (SANS-global) equal or higher than 10. Patients hospitalized in psychiatry units within 3 months prior to enrolment, treated with either injectable depot antipsychotic within 2 weeks prior to enrolment, or clozapine, olanzapine, risperidone or sertindole within the previous month, having severe risk of suicide or allergy, severe diseases other that schizophrenia deserving hospitalization within a term of 3 months, narrow-angle glaucoma, history or presence of unclassified seizures, leucopenia or jaundice, and pregnant women were excluded.

Treatment

Patients received doses of olanzapine or risperidone orally once daily, and the dose was left to the investigator's discretion. It was recommended to start olanzapine at 10 mg/day and risperidone at 3 mg/day, with a progressive tapering of previous antipsychotic medication. Investigators were allowed to make dosing adjustments based on clinical judgment without restriction to exceed the maximum dose recommended by the manufacturer. Biperiden (up to 6 mg/day) was allowed to treat treatment-emergent EPS, but not as a preventive treatment. Benzodiazepines/hypnotics were also allowed if clinically necessary.

Assessments

Patients were seen at monthly intervals up to week 24 and then every two months up to the end of randomized treatment, at week 48. Primary efficacy measure was the SANS global score and clinical response rate was defined as a reduction (≥ 30% in the SANS global score from baseline. Other measures were the Scale for the Assessment of Positive Symptoms[22] (SAPS) and the severity scale of the Clinical Global Impression (CGI-S) scale[23]. Adverse events and body weight were recorded in all visits. Vital signs were measured at weeks 8, 24, 48 (or withdrawal), and laboratory test controls were encouraged but left to the physician criteria. Extrapyramidal symptoms were systematically assessed with a questionnaire based on the UKU scale on EPS[24] in all study visits. Sexual dysfunction was evaluated by the Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ)[25].

Statistical methods

Statistical tests were performed at the 5%, two-tailed significance level for all data analyzed. Efficacy and sexual dysfunction analyses were performed in an intent-to-treat population, which included all randomized patients who received treatment and who had at least one post-baseline assessment available. Tolerability analysis was performed in a safety population, which comprised all randomized patients who received treatment. Between-group comparisons of change from baseline in continuous measures were analyzed using analysis of covariance with the treatment as the dependent variable, the centre as a factor and the baseline value as covariate in the model. Between-group, visit-wise comparisons were analyzed by repeated-measures analysis of variance considering the factors centre, visit, and treatment by visit interaction. Within-group changes from baseline were analyzed by a Wilcoxon test. Overall differences in categorical measures were analyzed by Mantel-Haenszel Chi-Square (or Fisher's exact test) controlling for centre. Changes from baseline were analyzed over imputed data (missing data estimated by last observation carried forward, LOCF); except for weight, for which analyses were done using both, observed and imputed data.

RESULTS

Patient characteristics and disposition

A total of 250 subjects were randomized. Three of them terminated before receiving study medication and a further 12 did not have any post-baseline efficacy data. Thus, the study comprises safety data from 247 subjects and effectiveness data from 235 subjects. Patients' baseline characteristics are summarized in table 1. Most participants were male (72.5%, N = 179) and their mean age was 36.3 years

Table 1 Baseline characteristics of patients

Characteristic	Olanzapine (N = 124)	Risperidone (N = 123)	*p* value
Age (years, mean [SD])	37 (10.6%)	35.5 (10.6%)	0.2679 (ANOVA)
Gender (N [%] of males)	85 (68.5%)	94 (76.4%)	0.1660 (Chi-square)
Schizophrenia subtype (N [%])			0.4415 (Fisher)
Catatonic	1 (0.8%)	0 (0%)	
Disorganized	7 (5.6%)	0 (0%)	
Undifferentiated	11 (8.9%)	21 (17.1%)	
Paranoid	82 (66.1%)	77 (62.6%)	
Residual	23 (18.5%)	25 (20.3%)	
Age at clinical onset (years, mean [SD])	23.7 (6.8%)	24.0 (7.1%)	0.7997 (ANOVA)
Weight (kilograms, mean [SD])	73.8 (14%)	80.5 (15.6%)	0.0005 (ANOVA)
SANS global score (LSM [SE])	14.14 (0.26%)	14.06 (0.27%)	0.8089 (ANOVA)
CGI score (mean [SD])	4.5 (0.7%)	4.4 (0.8%)	0.7564 (ANOVA)

LSM: least square mean; SE: standard error; SD: standard deviation.

(SD = 10.6). There were no significant differences between both treatment groups in baseline characteristics, with the exception of body weight that was significantly lower in the olanzapine-treated patients (olanzapine: mean: 73.8 [SD: 14]; risperidone mean: 80.5 [SD: 15.6]; $p < 0.001$).

A greater proportion of participants in the olanzapine group completed the study (87 out of 124 [70.2%] of the olanzapine-treated patients and 76 out of 123 [61.8%] of the risperidone-treated patients), although this difference was not significant ($p = 0.1649$). The median duration of treatment was 338 days (range: 1-435) among the olanzapine-treated patients and 336 (range: 2-399) among the risperidone-treated patients. Table 2 shows the reasons for premature discontinuation from the study. The reason for premature discontinuation most frequently reported was patient decision (10.5% [N = 13] among the olanzapine-treated patients, and 26% [N = 32] among the risperidone-treated patients).

Table 2 Reason for discontinuation from the study (N [%])

	Olanzapine (N = 124)	Risperidone (N = 123)
Patient decision	13 (10.5%)	32 (26%)
Investigator decision	8 (6.5%)	6 (4.9%)
Lost of follow-up	6 (4.8%)	8 (6.5%)
Adverse event	6 (4.8%)	6 (4.9%)
Failure to fulfill entry criteria	1 (0.8%)	4 (10.6%)
Sponsor decision	3 (2.4%)	1 (0.8%)
Protocol deviation	0 (0%)	2 (1.6%)
Death	0 (0%)	1 (0.8%)

Medication

The initial, modal, and final doses of study medication received by participants are presented in table 3. Initial dose was that prescribed at baseline, mean modal dose is calculated after computing the modal dose of each patient throughout the study, and final dose was that received at

Table 3 Initial, modal and final dose of olanzapine and risperidone in the study

	Olanzapine (N = 124)	Risperidone (N = 123)
Initial dose		
Mean (SD)	9.2 (4.2%)	3.6 (1.5%)
Median (range)	10 (1.2-30)	3 (1-6)
Modal dose		
Mean (SD)	12.3 (6.3%)	5.2 (2.5%)
Median (range)	10 (2.5-30)	6 (1-15)
Final dose		
Mean (SD)	12.1 (5.8%)	5 (2.2%)
Median (range)	10 (2.5-30)	4.9 (1-12.9)

the end of follow-up. The mean modal dose through the trial was 12.3 mg/day (SD: 6.3) of olanzapine and 5.2 mg/day (SD: 2.5) of risperidone. The distribution of the mean modal daily doses throughout the trial was less than 5 mg of olanzapine received by 1.6% of the olanzapine participants (N=2), 5-10 mg by 61.3% (N=76), 10-15 mg by 16.9% (N=21), 15-20 mg by 14.5% (N=18) and more than 20 mg by 5.6% (N=7), and less than 3 mg of risperidone received by 5.7% (N=7) of the risperidone participants, 3-6 mg by 80.5% (N=99), 6-9 mg by 8.9% (N=11) and more than 9 mg by 4.9% (N=6).

A significantly greater percentage of risperidone patients received anticholinergic medication (39% of risperidone-treated patients [N=48] and 25.8% of olanzapine-treated patients [N=32]; p=0.0264) and hypnotics (22.8% of risperidone-treated patients [N=29] and 5.6% of olanzapine-treated patients [N=7]; p=0.0001) during the study. Also, the number of days on anticholinergics was significantly greater among the risperidone-treated patients (number of days: mean: 121.7; SD: 121.9; median: 78.5, in the risperidone-treated patients versus mean: 35.4; SD: 65.9; median: 13.5 in the olanzapine-treated patients; p=0.0005).

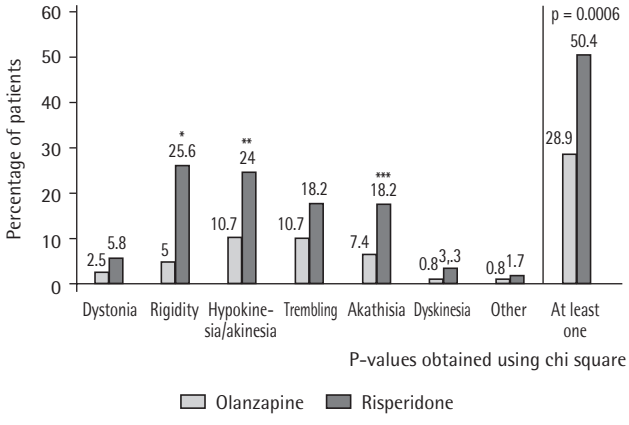

Figure 1 *Incidence of treatment emergent EPS or worsening of previous EPS systematically recorded by means of the UKU-based questionnaire throughout treatment with either risperidone (N=123) or olanzapine (N=124). *p< 0.001; **p=0.0103; ***p=0.0198.*

Extrapyramidal symptoms (EPS)

Extrapyramidal symptoms (akathisia, dysarthria, dyskinesia, dystonia, extrapyramidal disorder, hypokinesia, muscle rigidity, parkinsonism and tremor) were reported as treatment emergent adverse events by 27.63% (N=67) risperidone-treated patients and 9.7% (N=24) olanzapine-treated patients (p=0.0003). Individual EPS reported by significantly more risperidone patients were akathisia (1.6% of olanzapine-treated patients versus 7.3% of risperidone-treated patients; p=0.0029), tremor (13% of risperidone-treated patients, versus 3.2% of olanzapine-treated patients, p=0.0301) and muscle rigidity (6.5% of risperidone-treated patients, versus 0% of olanzapine-treated patients, p=0.0034).

The incidence of treatment emergent EPS or worsening of previous EPS systematically recorded by means of the UKU-based questionnaire was significantly greater with risperidone (50.4% [N=61] of risperidone-treated patients versus 28.9% [N=35] of olanzapine-treated patients; p=0.0006). By symptoms, rigidity (25.6% of risperidone-treated patients versus 5% of olanzapine-treated patients; p<0.001), hypokinesia/akinesia (24% of risperidone-treated patients versus 10.7% of olanzapine-treated patients; p=0.0103) and akathisia (18.2% of risperidone-treated patients versus 7.4% of olanzapine-treated patients; p=0.0198) were reported significantly by more risperidone-treated patients. No treatment-emergent EPS was reported more frequently in the group treated with olanzapine (fig. 1). No baseline differences between treatment groups were observed.

Adverse events

More risperidone-treated patients experienced at least one treatment emergent adverse event (62.9% [N=78] of olanzapine-treated patients versus 72.4% [N=89] of risperidone-treated patients), but difference between groups was not statistically significant. The adverse events occurring in ≥5% of participants in either group are shown in table 4. Anxiety, insomnia, and tremors were the most frequently reported adverse events. Tremors, akathisia and sexual dysfunction were significantly more frequent in patients treated with risperidone compared to patients treated with olanzapine. Out of the twelve (12) adverse events listed in table 4, headache, weight increased, hypertension, and appetite increased were more frequently reported in patients treated with olanzapine; however, the between treatment group incidences were not statistically significant. Adverse events related to the metabolism of carbohydrates were reported equally in both groups (diabetes mellitus in 0.8% [N=1] and hyperglycemia in 1.6% [N=2] of participants of each treatment group).

Weight gain

Although numerically greater in patients treated with olanzapine, mean gains in body weight did not differ significantly between treatment groups (mean: 3.8 [SD: 6.1] in

Table 4 Adverse events reported by 5% or more of study participants treated either with risperidone or olanzapine (N [%])

	Olanzapine (N = 124)	Risperidone (N = 123)	*p* value*
Anxiety	15 (12.1%)	17 (13.8%)	0.6866
Insomnia	8 (6.5%)	17 (13.8%)	0.0549
Tremor	7 (5.6%)	17 (13.8%)	0.0301
Libido decreased	7 (5.6%)	8 (6.5%)	0.7775
Akathisia	2 (1.6%)	11 (8.9%)	0.0099
Somnolence	5 (4.0%)	8 (6.5%)	0.3844
Headache	7 (5.6%)	5 (4.1%)	0.5636
Weight increased	8 (6.5%)	3 (2.4%)	0.1264
Hypertension	7 (5.6%)	4 (3.3%)	0.3620
Appetite increased	8 (6.5%)	2 (1.6%)	0.1023
Muscle rigidity	2 (1.6%)	8 (6.5%)	0.0596
Sexual dysfunction	1 (0.8%)	7 (5.7%)	0.0357

* Chi square.

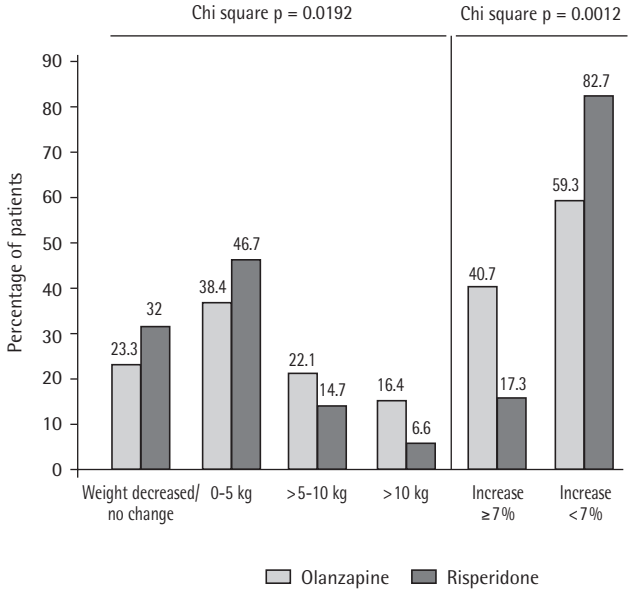

Figure 2 *Change from baseline in body weight of patients treated with either risperidone (N = 123) or olanzapine (N = 124).*

the olanzapine-treated patients and 2.1 kg [SD: 6] in the risperidone-treated patients; least square mean: 3.5 kg [SE: 0.62] and 2.97 kg [SE: 0.69], respectively; p = 0.5467). Maximum gains (from baseline to each patient's maximum gain) were neither significantly different between groups (mean: 5.3 kg [SD: 5.6] in the olanzapine-treated patients and 3.5 kg [SD: 5.3] in the risperidone-treated patients); but greater than end-of-study gains, probably because some patients were able to lose some of their initial gain while on treatment. Nevertheless, when study participants were categorized according to their changes from baseline in the body weight, an uneven distribution was found. Patients treated with risperidone had a higher incidence of no change/decrease in weight gain or increases lower than or equal to 5 kg compared to patients treated with olanzapine who showed a higher incidence of weight gain greater than 5 kg (p = 0.0192) (fig. 2). In addition, the proportion of patients with a weight increase from baseline of 7% or greater was significantly higher among the olanzapine-treated patients (40.7% [N = 35] versus 17.3% [N = 13] among the risperidone-treated patients; p = 0.0012) (fig. 2). The temporal evolution of weight gain was different between groups. Changes from baseline were significantly greater with olanzapine from week 8 to either week 16 or 24 (depending on the case set considered, observed or LOCF data, respectively); but not at further time points, indicating that gain occurred mainly at the beginning of treatment with olanzapine, while risperidone was associated with a more sustained linear weight gain (fig. 3).

Sexual dysfunction

Patients treated with olanzapine showed significantly greater reductions (improvement) from baseline in the PRSexDQ score (olanzapine: mean: 1.3 [SD: 3.7], risperidone: mean: 0.2 [SD: 3.5]; p = 0.0292). Adverse events related to the sexual dysfunction were significantly more frequently reported by risperidone patients (21.1% [N = 26] with risperidone versus 7.3% [N = 9] with olanzapine; p = 0.0018). The most frequent sexual adverse events were libido decreased (6.5% [N = 8] with risperidone versus 5.6% [N = 7] with olanzapine; p = 0.7775) and sexual dysfunction not specified (5.7% [N = 7] with risperidone versus 0.8% [N = 1] with olanzapine; p = 0.0357).

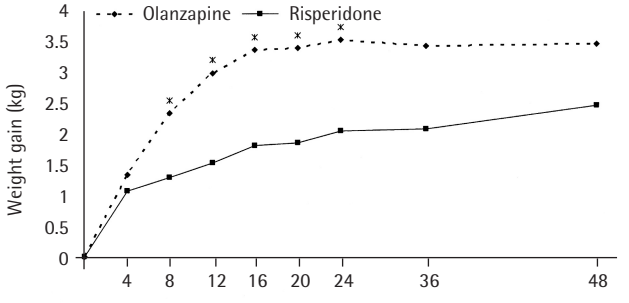

Figure 3 *Weight gain throughout treatment with either risperidone or olanzapine (by-visit LOCF). *p < 0.05 for between-group comparisons using ANCOVA.*

Efficacy

Patients treated with olanzapine showed statistically significant greater reductions from baseline in SANS global, total, and composite scores, in SAPS global, total and composite scores, and CGI-S scores than patients treated with risperidone (table 5). A higher proportion of olanzapine-treated patients showed clinical response, defined as a reduction (≥ 30% in the SANS global score from baseline (69.2% [N = 83] among the olanzapine-treated patients versus 48.7% [N = 56] among the risperidone-treated patients; p = 0.0014). Regarding the positive symptoms, the proportion of patients showing a reduction (≥ 30% in the SAPS global score from baseline was greater in the group treated with olanzapine, although the difference was not significant (72.4% [N = 84] among the olanzapine-treated patients versus 61.1% [N = 69] among the risperidone-treated patients; p = 0.0682).

CONCLUSIONS

The design of this study tried to minimize the drawbacks of previous head-to-head comparisons: this included a large sample size, a randomized allocation, a long follow-up period (one year), and a flexible dosing schedule extensive to initial doses and tapering of prior antipsychotic medications. In this way, it was conceived to complement the data yielded by olanzapine and risperidone clinical trials, providing valuable information for the clinician.

The safety profile obtained from patients treated with olanzapine is consistent with that observed in previous clinical trials and included in the product package insert. The most expected adverse events (> 10%) according to the European Summary of Product Characteristics (SPC) are somnolence and weight gain. The incidence of such events in this study is lower than that observed in the registration trials, but similar to that obtained in observational studies (somnolence 4% and weight gain 6.5%), and is probably closer to the real incidence of clinically significant cases of both events. Interestingly, in this trial the incidence of somnolence was slightly greater in patients treated with risperidone (6.5%), and mean weight gain was not significantly higher in olanzapine patients. Other adverse events frequently reported by olanzapine patients were anxiety (12.1%), insomnia (6.5%) and appetite increased (6.5%), but the incidence of none of them was significantly different than that reported with risperidone. The safety profile observed with risperidone is also consistent with the previous information. According to the SPC, the most common events are insomnia, agitation (or akathisia), anxiety and headache, reported by 13.8%, 8.9%, 13.8% and 4.1% of risperidone patients in this study, respectively. Other events frequently reported by risperidone patients were tremor (13.8%), somnolence (6.5%), muscle rigidity (6.5%) and sexual dysfunction (5.7%). Tremor, akathisia and sexual dysfunction were reported by significantly more risperidone-treated patients.

The results of this study indicate that olanzapine is temporally associated with a decreased incidence of the number of treatment-emergent EPS compared with risperidone. Criticism was made to previous reports from head-to-head comparisons that also claimed this advantage[15,16,18] on the basis that they used risperidone doses higher than those selected for use in clinical practice[17]. The mean modal daily dose of risperidone received by participants in this study was 5.2 mg, and this was adjusted according to routine

Table 5 Reduction from baseline in effectiveness measures

Measure	Olanzapine (N = 120)		Risperidone (N = 115)		*p* value*
	Baseline	Reduction	Baseline	Reduction	
SANS-global (LS mean [SE])	14.14 (0.26)	5.93 (0.4)	14.06 (0.27)	4.53 (0.4)	0.0151
SANS-total (LS mean [SE])	77.33 (1.60)	32.59 (2.3)	76.56 (1.63)	24.97 (2.4)	0.0168
SANS-composite (LS mean [SE])	63.18 (1.37)	26.65 (2.0)	62.50 (1.40)	20.45 (2.0)	0.0183
SAPS-global (LS mean [SE])	6.60 (0.31)	3.31 (0.3)	5.93 (0.32)	2.41 (0.3)	0.0207
SAPS-total (LS mean [SE])	36.00 (1.83)	18.98 (1.5)	32.89 (1.87)	13.65 (1.6)	0.0116
SAPS-composite (LS mean [SE])	29.40 (1.54)	15.66 (1.2)	26.96 (1.58)	11.25 (1.3)	0.0115
CGI-S (mean [SD])	4.40 (0.70)	1.0 (1.0)	4.40 (0.80)	0.6 (1.1)	0.0082

* ANCOVA. LS mean: least square mean; SE: standard error; SD: standar deviation.

practice; with 86.2 % of risperidone patients receiving mean modal daily doses equal or lower than 6 mg/day throughout the study. However, despite the relatively low doses of risperidone, the incidence of EPS were greater in the group treated with this drug.

This study provides useful long-term data about the issue of weight gain. Although absolute weight increases in patients treated with olanzapine were higher than in those treated with risperidone, overall differences at the end of the study were not significantly different. Olanzapine was associated with a quick gain after treatment onset while risperidone-treated patients showed a slow but continuous gain. Significant differences favoring risperidone were present along the first half of the study (shorter when only observed data are considered), as the mean body weight gain in the group receiving olanzapine stabilized after week 20 whilst in the group treated with risperidone it continued rising. One possible explanation for the divergence between observed and carried-over data is that some olanzapine-treated patients would have left the study in the first weeks because of weight gain. Also, significantly more patients treated with olanzapine showed a weight increase ≥ 7 %, but this result could be influenced by the statistically significant higher baseline mean body weight observed in risperidone patients. The long-term outcome is relevant for the assessment of the risk-benefit ratio of therapeutic alternatives in a disease, like schizophrenia, that requires chronic treatment.

Interferences with glucose metabolism have been reported with atypical antipsychotics. Although cases attributed to dibenzodiazepine agents (clozapine and olanzapine) are more numerous than those associated with risperidone[26], the number for risperidone-associated hyperglycemia has been also found to be relatively higher than that observed with the first generation agents[27]. However, reports in the literature are limited to personal observations or database research; thus, prospective data is awaited. In the present study, neither drug was associated with carbohydrate metabolism dysfunction; only three cases of new onset hyperglycemia (one for olanzapine and two for risperidone) have been reported, of which only one in the risperidone group was considered treatment-emergent.

Olanzapine yielded an improved sexual function and statistically significant less adverse events related to the sexual function than risperidone, confirming the well-known potential for hyperprolactinemia of risperidone.

Olanzapine procured a greater improvement than risperidone in the primary measure of efficacy, the SANS global score. Statistically significant greater improvements with olanzapine were also seen in the composite and total SANS scores, which provide a more objective assessment. Of note, and in contrast with previous reports[28,29], olanzapine achieved also a significantly better improvement in positive symptoms as measured by the SAPS, perhaps due to the residual characteristics of these positive symptoms in a specific population of stabilized out patients with prominent negative symptoms. In fact, olanzapine has shown non-inferiority to clozapine in the treatment of residual positive symptoms in refractory patients[30]. Response rates both in terms of positive or negative symptoms were also higher in the olanzapine group; although the differences between groups only reached statistical significance in the case of negative symptoms.

This study provides valuable information for the decision-making process in adjusting antipsychotic pharmacotherapy. While both treatments have proven to be effective and acceptably safe in patients with schizophrenia, achieving significant and clinically relevant improvements in psychopathology, some features of this study are notable. First, participants were outpatients with prominent negative symptoms in stable condition but still with a residual positive component after optimization of previous therapy with first-generation antipsychotic agents. Second, this study was conducted without constraining the dose or the schedule of visits and without controlling treatment compliance beyond the standard in the routine care. While controlled clinical trials tell us more about a drug, naturalistic studies provide valuable information about the interaction between the drug, the illness, and the patient in real life, and data are thus useful in dealing with patients' and clinicians' concerns. In addition, it has the advantages of a randomized allocation. Third, this was a long-term, prospective study. Large, long-term, randomized studies in schizophrenia are overdue as the ambition of therapeutic goals grow, requiring complex and enduring endpoints for their evaluation.

Both olanzapine and risperidone were safe and well tolerated as well as efficacious in the treatment of this population of stabilized outpatients with schizophrenia with prominent negative symptoms. Olanzapine was temporally associated with a decreased incidence of treatment-emergent EPS and sexually-related adverse events. The mean body weight increase with both drugs were comparable after one year, although patients treated with olanzapine presented a significantly higher incidence of clinically important body weight increase (≥ 7 % from baseline) than risperidone. Other adverse events were evenly distributed between treatment groups. Additionally, olanzapine showed advantage over risperidone in further improvement in both negative and positive symptoms.

ACKNOWLEDGMENTS

This clinical trial has been funded by Laboratorio Lilly, S.A.

REFERENCES

1. Kane JM. Schizophrenia. N Eng J Med 1996;334:34-41.
2. Kane JM. Clinical efficacy of clozapine in treatment-refractory schizophrenia: an overview. Br J Psychiatry 1992;160(Suppl. 17): 41-5.
3. Lieberman JA. Prediction of outcome in first-episode schizophrenia. J Clin Psychiatry 1993;54:13-7.
4. Corrigan PW, Liberman RP, Engel JD. From non-compliance to collaboration in the treatment of schizophrenia. Hosp Community Psychiatry 1990;41:1203-11.
5. Meltzer HY. The mechanism of action of novel antipsychotic drugs. Schizophr Bull 1991;17:263-87.
6. Kinon BJ, Lieberman JA. Mechanisms of action of atypical antipsychotic drugs: a critical analysis. Psychopharmacology 1996; 124:2-34.
7. Tandon R, Jibson MD. Efficacy of newer generation antipsychotics in the treatment of schizophrenia. Psychoneuroendocrinology 2003;28(Suppl. 1):9-26.
8. Chouinard G, Jones B, Remington G, Bloom D, Addington D, MacEwan GW, et al. A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. J Clin Psychpharmacol 1993;13:25-40.
9. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. Am J Psychiatry 1994;151:825-35.
10. Peuskens J. Risperidone in the treatment of patients with chronic schizophrenia: a multi-national, multi-centre, double-blind, parallel-group study versus haloperidol. Risperidone Study Group. Br J Psychiatry 1995;166:712-726
11. Beasley CM Jr, Tollefson G, Tran P, Satterlee W, Sanger T, Hamilton S. Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. Neuropsychopharmacology 1996;14:111-23.
12. Beasley CM Jr, Sanger T, Satterlee W, Tollefson G, Tran P, Hamilton S. Olanzapine versus placebo: results of a double-blind, fixed-dose olanzapine trial. Psychopharmacology 1996;124:159-67.
13. Tollefson GD, Beasley CM Jr, Tran PV, Street JS, Krueger JA, Tamura RN, et al. Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. Am J Psychiatry 1997;154:457-65.
14. Tollefson GD, Sanger TM. Negative symptoms: a path analytic approach to a double-blind, placebo- and haloperidol-controlled clinical trial with olanzapine Am J Psychiatry 1997;154:466-74.
15. Tran PV, Hamilton SH, Kuntz AJ, Potvin JH, Andersen SW, Beasley C Jr, et al. Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. J Clin Psychopharmacol 1997;17:407-18.
16. Ho BC, Miller D, Nopoulos P, Andreasen NC. A comparative effectiveness study of risperidone and olanzapine in the treatment of schizophrenia. J Clin Psychiatry 1999;60:658-63.
17. Conley RR, Mahmoud R. A randomized double-blind study of risperidone and olanzapine in the treatment of schizophrenia or schizoaffective disorder. Am J Psychiatry 2001;158:765-74.
18. Gureje O, Miles W, Keks N, Grainger D, Lambert T, McGrath J, et al. Olanzapine vs risperidone in the management of schizophrenia: a randomized double-blind trial in Australia and New Zealand. Schizophr Res 2003;61:303-14.
19. Gomez JC, Sacristán JA, Hernández J, Breier A, Ruiz Carrasco P, Antón Saiz C, et al for the EFESO Study Group. The safety of olanzapine compared with other antipsychotic drugs: results of an observational prospective study in patients with schizophrenia (EFESO Study). J Clin Psychiatry 2000;61:335-43.
20. Alvarez E, Bobes J, Gómez JC, Sacristán JA, Cañas F, Carrasco JL, et al. for the EUROPA Study Group. Safety of olanzapine versus conventional antipsychotics in the treatment of patients with acute schizophrenia. A naturalistic study. Eur Neuropsychopharmacol 2003;13:39-48.
21. Andreasen NC. The scale for the assessment of negative symptom (SANS): conceptual and theoretical foundations. Br J Psychiatry 1989;155:S49-52.
22. Andreasen NC. Methods for assessing positive and negative symptoms. Mod Probl Pharmacopsychiatry 1990;24:73-88.
23. Guy W. ECDEU Assessment Manual for Psychopharmacology, Revised Version. Bethesda: US Department of Health, Education and Welfare, 1976; 217-22.
24. Lingjaerde O, Ahlfors UG, Bech P, Dencker SJ, Elgen K. The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. Acta Psychiatr Scand Suppl 1987; 334:1-100.
25. Montejo AL, García M, Espada M, Rico-Villademoros F, Llorca G, Izquierdo JA. Psychometric characteristics of the psychotropic-related sexual dysfunction questionnaire. Spanish work group for the study of psychotropic-related sexual dysfunctions. Actas Esp Psiquiatr 2000;28:141-50.
26. Fuller MA, Shermock KM, Secic M, Grogg AL. Comparative study of the development of diabetes mellitus in patients tak-

ing risperidone and olanzapine Pharmacotherapy 2003;23: 1037-43.

27. Koller EA, Cross JT, Doraiswamy PM, Schneider BS. Risperidone-associated diabetes mellitus: a pharmacovigilance study. Pharmacotherapy 2003;23:735-44.

28. Bailer J, Braüer W, Rey ER. Premorbid adjustment as predictor of outcome in schizophrenia: results of a prospective study. Acta Psyciatric Scandinavica 1996;93:368-77.

29. Jackson HJ, Minas IH, Burgess PM, Joshua SD, Charisiou J, Campbell IM. Negative symptoms and social skills performance in schizophrenia. Schizophr Res 1989;2:457-63.

30. Tollefson GD, Birkett MA, Kiesler GM, Wood AJ, Lilly Resistant Schizophrenia Study Group. Double-blind comparison of olanzapine versus clozapine in schizophrenic patients clinically eligible for treatment with clozapine. Biol Psychiatry 2001;49: 52-63.