Efficacy and safety of olanzapine in the treatment of schizophrenia (ESOLAS study)

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Summary

Background: To determine the efficacy and safety of olanzapine (Zalasta®/Zolrix®) in patients with schizophrenia.

Subjects and methods: The sample included 99 patients with schizophrenia according to the ICD-10 criteria. All patients were treated with olanzapine in flexible doses, with the average dose of 13.54 mg daily over an 8-week period. Efficacy measurements included Positive and Negative Syndrome Scale (PANSS), Clinical Global Impressions-Improvement Scale (CGI-I) and Clinical Global Impressions-Severity of Illness Scale (CGI-S), and Barnes Akathisia Scale. Safety measurements included weight, waist circumference, blood pressure, and heart rate. All scales and safety measurements were administered at baseline and at weeks 2, 4 and 8.

Results: After 8 weeks of treatment with olanzapine, a total of 91 patients (91.9 %) completed the study. At week 8, olanzapine treatment resulted in a statistically significant decrease in PANSS scores (from 98.99±18.93 to 66.81±15.36; p<.0001), a statistically significant decrease of positive and negative subscales scores (p<.0001), and hostility, anxiety and depression items (p<.0001). Olanzapine treatment resulted also in a statistically significant decrease of CGI-S scores to 3.21±0.7 (from markedly ill to mildly ill) at week 8 (p<.0001). A significant improvement of the patients' overall condition towards the end of the study was observed on the CGI-I scale where 81 patients (88%) were rated by the physicians as »much/very much improved«. A significant improvement of akathisia was observed at the end of the study (p<.0001). After 8 weeks of treatment, weight, Body Mass Index, and waist circumference increased significantly (p<.0001); diastolic blood pressure significantly decreased (p<.0005) but systolic pressure and heart rate did not (p>.05).

Conclusion: Data from this study indicate that olanzapine is an efficient and safe therapeutic option for patients with schizophrenia.

Key words: olanzapine, schizophrenia, antipsychotic treatment

Introduction

Schizophrenia is a debilitating disease, ranked among the top 20 causes of disability worldwide (Vos et al. 2012). The illness impacts all aspects of a patient's life and alters perception of self and of the outside world.

Advances in the treatment of schizophrenia and earlier attention to diagnosis may lead to improved long-term outcomes and to a broader focus on effectiveness. An adequate treatment within the early stages of schizophrenia is of great importance in terms of the course and outcome of the illness. There is even greater focus on remission and partial functional recovery (Montgomery et al. 2012). The Schizophrenia Working Group defined remission as a state in which a person with schizophrenia experiences an improvement in core signs and symptoms such that the remaining psychiatric symptoms are of low intensity and no longer interfere significantly with behaviour (Andreasen et al. 2005).

Several studies have found that about 70% of patients fail to experience at least minimal response early in the treatment; nevertheless, currently available medications for schizophrenia are effective for only about 50% of the patients (Case M, et al. 2011). A recent meta-analysis of comparisons of second-generation antipsychotics in the treatment of schizophrenia has shown that olanzapine is superior to aripiprazole, quetiapine, risperidone and ziprasidone (Leucht et al. 2009).

The purpose of our study was to evaluate the efficacy and safety of olanzapine treatment in patients with the first or recurrent episodes of schizophrenia.

Subjects and methods

Participants

A naturalistic, multicenter, and open-label 8-week clinical study was conducted by Slovenian and Romanian psychiatrists. The main objective of this study was to determine the efficacy and safety of olanzapine in the treatment of patients with schizophrenia according to ICD-10 criteria. The study was approved by the Slovenian and Romanian Ethic Committee. Written informed consent was obtained from all patients prior to entry in the study. The study included out- and in-patients of both genders, 18 years and older, with the diagnosis of first episode of schizophrenia or a relapse of schizophrenia.

Patients that were hypersensitive to olanzapine or expedients, patients who were receiving other antipsychotics, pregnant or nursing women, and women with no contraception were not included in the study. All specifics included in the SPC were taken into account.

Methods

Starting dose of olanzapine was flexible with regard to the clinical picture, both at first visit (baseline) and throughout the study, dependent on the investigator's clinical judgment.

Efficacy assessments included The Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987), and the Clinical Global Impressions-Improvement scale (CGI-I) and the Clinical Global Impressions-Severity of Illness scale (CGI-S) (Guy 1976). Statistical analysis also included the following items: hostility, anxiety and depression. Follow-up visits were scheduled at weeks 2, 4 and 8.

Tolerability and safety measurements included recording and evaluation of reported adverse events, withdrawal and drop-outs, and the effects of treatment on physical variables, such as weight and body mass index, waist circumference, systolic and diastolic blood pressure, and heart rate. Barnes Akathisa Rating Scale was used for the assessment of akathisia (Barnes 1989).

Statistical analysis

The parameters used for clinical assessment of the treatment are considered to be ordinal or interval scale random variables. As common in statistical practice, »score« type parameters with a large range of possible values are sometimes considered to be ratio scale variables as blood pressure, heart rate etc. Analysis of the variables were calculated and statistic are presented: the least and the largest variables, the average (arithmetic mean), standard deviation and the standard error of mean. Because of the reasonably large sample, the asymptotic z-test is employed to assess the difference between means of two variables measured in the same population. An asymptotic 95%-confidence interval for the difference between means is used for interval estimation.

Results

The study sample consisted of 99 patients, but only 92 out- and in-patients with schizophrenia were included in the statistical analysis. Two were excluded

due to non-compliance and 5 due to protocol violation. The mean age of patients was 40.9±12.4 years. Men represented 38 % of the study population. Psychopathological symptoms that had lasted for over 2 months were present in 18 patients (20%). Some of the sociodemographic and clinical data are presented in Table 1.

During the past 15 days, 20 patients (21.7%) were receiving psychotropic medication (haloperidol, diazepam, risperidone, quetiapine, aripiprazole, amisulpride, valproate or escitalopram), and 72 patients (78.3%) did not. At the beginning of the study 89 patients (96,7%) were without other psychotropic concomitant therapy and only 3 patients were receiving nonpsychiatric concomitant therapy (trimetazidine/lisinopril, indapamide/perindopril, ranitidine, tramadol, and diclofenac).

At the baseline visit the average dose of olanzapine was 12.23 mg daily and was increased to 13.88 mg daily at the end of the study. At that time 75 patients (81.5%) were treated with orodispersible tablets of olanzapine instead of conventional tablets.

Mean baseline PANSS score was 98.99±18.93, with the mean baseline positive scale score of 26.17±4.47 and the mean baseline negative scale score of 24.18±5.52. Olanzapine treatment was followed with a statistically significant decrease of PANSS score to 66.81±15.36 (p<.0001) with a relative reduction by 32.3±9.95% at week 8. Positive scale scores decreased with statistical significance after 8 weeks to 15.45±4.25 (p<.0001) with relative reduction by 40.4±14.3%, and negative scale scores to 18.28±4.72 (p<.0001), with relative reduction by 24±13.32%. Baseline hostility mean score was 3.35±1.2 and was decreased to 2.03±0.86 (p<.0001) at week 8. After an 8-week treatment period, statistically significant improvement was observed also on the anxiety item (3.82±1.31 vs. 2.26±0.87) (p<.0001), and on the depression item (2.45±1.49 vs. 1.75±0.87) (p<.0001).

Mean baseline CGI-S score was 4.93±0.82 (markedly ill). Olanzapine treatment resulted in a statistically significant decrease of CGI-S scores to 3.21±0.7 (mildly ill) at week 8 (p<.0001). A significant improvement of the patients' condition towards the end of study was observed also on the CGI-I scale where 81 patients (88%) were rated by the physician as »much/very much improved« (Table 2).

A significant improvement of akathisia (assessed with Barnes Akathisa Rating Scale) with statistical significance was observed at the end of the study, since the average value of BARS during the first visit was 1.12±1.89 and after 8 weeks of treatment 0.54±1.26 (p<.0001). The analysis of how well patients tolerated olanzapine included 92 patients. Patients tolerated olanzapine well since 87% of patients in all periods experienced no adverse reactions. Adverse reactions occurred in 12 patients, which represents 13%. The most frequent mild to moderate adverse effects were somnolence (7.6%) and headache (3.3%). Only 1 patient discontinued treatment due to adverse reactions.

After 8 weeks of treatment, a statistically significant increase in body weight (from 69.8±14.04 kg to 72.7±14.2 kg; p<.0001), Body Mass Index (from 24.2±4.1 to 25.3±4.31 kg/m2; p<.0001), and waist

Variables	Study population, N=92
Gender, men, N (%)	35 (38)
Mean age, years	40.9±12
Psychotropic medication in the last 15 days, N (%)	20 (21.7)
Concomitant medication, N (%)	3 (3.3)
Smokers, N (%)	43 (47)
Alcohol consumers, N (%)	F 16 (17.4)

Table 1. *Sociodemographic data.*

PANSS	99±18.9	87.8±18.9	77.1±17.9	66.8±15.3
PANSS positive scale	26.1±4.4	22.0±4.5	18.7±4.5	15.5±4.3
PANSS negative scale	24.1±5.5	22.5±5.8	20.4±5.6	18.2±4.7
Hostility item	3.3±1.2	2.8±1.1	2.3±0.9	2.0±0.8
Anxiety item	3.8±1.3	3.0±1.0	2.6±0.9	2.2±0.8
Depression item	2.4±1.4	2.2±1.2	1.9±1.0	1.7±0.8
CGI-S	4.9±0.8	4.4±0.7	3.7±0.7	3.2±0.7
Follow-up visits: p<.0001 from baseline to week 8 on all measures.				

Table 2. *Primary and secondary outcome measures (N=92).*

circumference (from 86.95±11.95 cm to 89.82±12.26 cm; p<.0001) was observed. Diastolic blood pressure significantly decreased (p<.0005) but systolic pressure and heart rate did not (p>.05). (Table 3, 4).

Discussion

The aim of the ESOLAS study was to assess safety and efficacy of olanzapine in patients with schizophrenia in Slovenia and Romania. Baseline PANSS mean total score was 99 and was by the end of the 8-week trial reduced by 32 % which is consistent with other studies and can be associated with greater total predictive accuracy (Kinon et al. 2008a; Kinon et al. 2008b; Hatta et al. 2011; Case et al. 2011). The remission is an achievable goal and is necessary but it is neither a sufficient step toward recovery nor a static process (Kelly, et al. 2009). In our study patients responded early to the treatment since at the end of the 8-week study period 88 % of patients were assessed as »much/very much improved«.

Significant overall improvement from baseline was also observed regarding hostility, anxiety, and depression in our study. The resolution of depression symptoms may be an important factor in achieving remission (Kelly et al., 2009). The remission of depression symptoms in schizophrenia correlated with greater life satisfaction, better family relationships, and fewer alcohol-related problems and with a lower risk for suicidal behaviours (Ascher-Svanum, et al. 2005). Better scores on the positive, negative, hostility and depression subscales can be associated with higher productivity levels and better treatment compliance in patients with schizophrenia. In Liu-Seifert et al. study, patients treated with olanzapine experienced significantly greater improvement in productivity when compared to the patients treated with risperidone or ziprasidone (Liu-Seifert et al., 2011). For these reasons, more attention should be focused on different symptoms in schizophrenia.

The rate of the treatment discontinuation due to non-compliance was very low (only two patients were non-compliant). Prior research demonstrated that continuing or discontinuing antipsychotic medication is driven primarily by medication efficacy (Lieberman et al., 2005; Liv-Seifert et al., 2005). The majority of clinical studies concerning the efficacy and safety associated with olanzapine treatment have been conducted with SOT (standard olanzapine film-coated tablets) and only few with ODT (olanzapine orodispersible tablets). It appears that ODT may have an additional adherence advantages over SOT (Bitter et al., 2010). ODT may have some other advantages in clinical utilisation of olanzapine: rapid effects in acute agitation, easy dissolution, no need for additional liquids, etc. (Montgomery et al. 2012).

A significant improvement of akathisia (assessed with Barnes Akathisia Scale) was observed at the end of our study. In the Emsley study, achieving remission was associated with the improvement of extrapyramidal side effects which suggests that treatment with a better neurological side effects profile may be more likely associated with long-term improvement (Emsley et al. 2007).

Weight gain and co-morbid metabolic problems are regarded as the major issues associated with second generation antipsychotics. Generally, olanzapine and clozapine were found to be associated with the highest risk of clinically significant weight gain, followed by quetiapine, risperidone, and sertindole. Some findings show that sedating, low potency, first-generation antipsychotics also cause weight gain and that the dichotomy between first-generation and second-generation antipsychotics based on weight gain is another oversimplification (Leucht et al., 2013). In our study, mean weight gain after 8 weeks was 3 kg which is much less than a 6 kg weight gain according to the pooled data of clinical trials with multiple doses of olanzapine (Newcomer & Haupt, 2006) Waist

Visit	W (kg)	p-value	BMI (kg/m2)	p-value	WC (cm)	p-value
Baseline	69.8±14		24.1±4.2		86.9±11.9	
Week 8	72.7±14.1	p<0.0001	25.3±4.3	p<.0001	89.8±12.3	p<0.0001

Table 3. *Metabolic variables (W – weight; BMI – Body Mass Index; WC – waist circumference).*

Visit	SBP (mmHg)	p-value	DBP (mmHg)	p-value	HRT (b.p.m)	p-value
Baseline	121.7±7.8		74.5±7.5		76.8±8	
Week 8	120.4±7.5	p=NS	71.7±7.6	p<.0005	76.7±6	p=NS

Table 4. *Cardiovascular parameters (SBP – systolic blood pressure; DBP – diastolic blood pressure; HRT – heart rate).*

circumference can be a valuable screening tool in the prediction of obesity (Hatta, et al. 2009). The review by Leucht et al. concluded that in tailoring drug treatment to the individual patient, small efficacy superiorities must be weighed against large differences in side-effects and cost (Leucht, et al., 2009).

The safety of olanzapine was assessed on the basis of causally related adverse reactions where it transpired that 87% of patients treated experienced no adverse reactions and other 13% experienced mild side effects as somnolence and headache.

Our study show some limitations, the most obvious being the open-label design of the study.

Conclusion

In conclusion, the data from our study, placed in real clinical setting, indicate that olanzapine is an efficient and safe therapeutic option for patients with schizophrenia, either with the first or a recurrent episode.

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