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Randomized trial of clozapine vs. risperidone in treatment-naïve first-episode schizophrenia: Results after one year

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ABSTRACT

In first-episode patients with psychosis, clozapine may be potentially valuable as an initial treatment seeking to limit early on clinical and cognitive deterioration. Nevertheless, until recently its restricted use has limited the study of this possibility. Our research group is developing a non-commercial, multicentric and open label study on the differential efficacy between clozapine and risperidone in first-episode schizophrenia. In this paper, we present the results related to clinical variables after a one-year follow-up. So far, we have recruited 30 patients diagnosed with schizophrenia or schizophreniform disorder with illness duration of less than two years. The patients had not received any previous treatment and they were randomized to treatment with clozapine or risperidone. Our results indicate that on average, patients on clozapine adhered to their original treatment for a longer time period than patients on risperidone. By last observation carried forward (LOCF) analysis, patients on clozapine and risperidone displayed similar clinical improvements, although marginally greater improvements in positive and total symptoms scores were found in the clozapine group. At the 12-month point we observed a marginal improvement in negative symptom scores in patients on clozapine. Subjective secondary effects, as measured with the Udvalg for KliniskeUndersøgelser (UKU) scale, correlated negatively with negative symptoms at follow-up. Our data, although preliminary, suggest that clozapine may have a slightly superior efficacy in the initial year of treatment of first-episode treatment-naïve patients with schizophrenia, and this can be explained for the most part by greater adherence to this treatment.

1. Introduction

Most patients with schizophrenia present cognitive and socio-occupational impairment (Cook and Razzano, 2000; Modestin et al., 2003; Sharma and Antonova, 2003; Priebe, 2007), especially at illness onset (Mason et al., 1996). Early intervention studies failed to provide firm results in favor of a determined drug that targets cognitive and socio-occupational impairment prevention (Crossley et al., 2010; Crespo-Facorro et al., 2012). The possibility of using clozapine as a first option treatment in the initial stages of schizophrenia has been proposed long ago (Angst et al., 1971; Hofer et al., 2003; Woerner et al., 2003; Shaw et al., 2006) looking to avoid a supposed "toxicity" of the psychosis with the pharmacological treatment that better reduces the severity of psychotic symptoms (Green and Schildkraut, 1995; Agid et al., 2010). However, the past and current limitations on its use have hampered a full exploration of this alternative (Kolivakis et al., 2002).

We are only aware of one study in which first-episode patients with psychosis received clozapine without ever being treated with any other pharmacological treatment (Lieberman et al., 2003). In this seminal work, researchers compared clozapine and chlorpromazine for the duration of 52 weeks with a prospective, randomized and double-blind approach. Subsequently, the sample was tracked for nine years (Girgis et al., 2011); resulting in greater time in remission with clozapine that was not observed after one year follow-up or in the long-term. The sample was recruited in China, with certain unusual characteristics for our environment, such as: the prolonged duration of the hospitalizations, the late age-onset, the massive acceptance of inclusion and the adherence to treatment. For all of this, it might be interesting to replicate these findings in our setting.

With our present work we aimed towards examining if first-episode patients with psychosis, initially treated with clozapine, evolved more favorably than patients treated with a drug usually

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prescribed in these cases in our setting, such as risperidone. This paper is a communication of the results after the first year of a two-year follow-up design, in which neuropsychological and neuroimaging aspects will also be taken into account in further analyses.

2. Materials and methods

2.1. Framework

The study was carried out in Madrid and the patients were recruited from the area of influence of the 12 de Octubre Hospital, along with the Jiménez Díaz Foundation, Infanta Cristina Hospital and Gregorio Marañón Hospital. The ethical boards of these institutions approved the study. Since the use of clozapine was beyond its regular indication we designed a clinical trial approach authorized by the Spanish Agency of Medicine and Sanitary Products (AEMPS) (registered in the clinical trials data base of the European Medicines Agency as EUDRACT No.: 2006-002000-34). This clinical trial was developed without any commercial interests, and completely financed from public agencies: the Social Security's Health Research Fund and the Ministry of Health and Social Policy, the Advanced Therapies and Transplants National Agency.

2.2. Participants

The patients were included after written acceptance of the corresponding informed consent form. The inclusion criteria were as follows: (i) diagnosis of schizophrenia or schizophreniform disorder (according to DSM-IV criteria), with less than two years of evolution and without any previous treatment; (ii) absence of any other psychiatric disorder (Axis 1 or focal neurological signs); (iii) absence of psychotropic drugs one month before the study commencement, or antidepressants in the three months prior to inclusion; (iv) the absence of cranial trauma or infection of the central nervous system; (v) absence of drug dependency, including alcohol but, with the exception of nicotine and caffeine; and (vi) age below 35 years in males and 40 years in females.

From a total of 53 contacted patients, 33 (62.2%/21 males) agreed to inclusion. Three patients (two of them with risperidone) were excluded during follow-up for not evolving to a diagnosable schizophrenia disorder (delusional disorder, manic-depressive disorder with psychotic symptoms, and psychosis due to cocaine). Out of the 30 remaining patients, equally and randomly distributed to each drug therapy, seven patients (five of them on risperidone) abandoned the study without further explanation, and three patients (two from the risperidone group) were excluded for an absence of response and intolerance to treatment.

A total of six patients switched treatments during follow-up of the study. Two patients agreed to switch from risperidone to clozapine at weeks 3 and 5 because of manifest lack of improvement. Another two agreed to switch to clozapine at month 8 because they failed to adhere to risperidone and relapsed, the lack of adherence being secondary to intolerance. Two cases agreed to switch from clozapine to risperidone at months 8 and 9 after they failed to adhere to clozapine and relapsed. Data of these cases were only used in the last observation carried forward (LOCF) analyses within the group of the original drug.

2.3. Procedure and tools of assessment

After signing informed consents, the patients who met the inclusion criteria were randomly assigned a treatment of risperidone or clozapine. Upon acceptance, the treatment was assigned according to arrival order of the patients, i.e., even cases were assigned to the clozapine arm and odd cases to the risperidone arm, without allocation concealment. This study seeks to assess results in real treatment conditions. Therefore, even though patients were assessed according to protocol, they maintained regular clinical attention as usual in their corresponding mental health centers. In most cases the protocol included two and a half weeks of hospitalization and a follow-up on outpatient basis; made up of appointments with the psychiatrist, health-care programs and psychoeducational support.

For clinical assessment, we employed the Positive and Negative Syndrome Scale (PANSS; (Kay et al., 1987)), and the Udvalg for KliniskeUndersøgelser (UKU) Side Effects Rating Scale (Lingjaerde et al., 1987); applied at weeks 1, 2, 3, 4, 6, 8, 10 and 12, and months 6, 12, 18 and 24. The dosage of the treatment was prescribed according to the patient's situation as usual in clinical practice (started at 12.5 mg a day, maximum dosage of 900 for clozapine; started at 2 mg, maximum dosage of 10 for risperidone). The mean dosage employed at week 12 was 5.22 (sd 0.97; range: 4–6) for risperidone, 226.66 (sd: 97.95; range: 100–400) for clozapine; and after one year: 5.43 (sd: 1.51; range: 4–8) for risperidone and 220.45 (sd: 112.26; range: 25–350) for clozapine.

We monitored weight, electrocardiogram, control of lipids and glycemia at baseline and week 12 (they would be re-assessed by month 24). Patients treated with clozapine followed standard blood-cell count protocol.

Patients were excluded from the study for the following reasons: not evolving to a diagnosable schizophrenia disorder, withdrawal of consent, non-fulfillment of treatment, follow-up protocol violation, pregnancy, important adverse occurrences (defined according to the "Norms of Good Clinical Practice", of the Spanish Agency for Drugs and Health Products AEMPS (AEMPS, 2008)) or therapeutic failure (defined as an increase of 50% of the total PANSS scores with respect to baseline, with scores higher or equal to "Moderate" (=4) in the items of the positive subscale; with a duration of more than two weeks) during follow-up.

2.4. Statistics

Baseline demographic, clinical and metabolic parameters were compared between clozapine and risperidone treated patients by Mann–Whitney U-test or X^2-test, when appropriate.

In order to test differences in efficacy between clozapine and risperidone in first-episode patients, we compared the outcomes in both patients groups as follows:

First, we analyzed the differences between groups (clozapine and risperidone) in number of drop-outs and treatment switches (X^2 tests), and the time from inclusion to drop-out in weeks (Mann–Whitney U tests).

Second, for within and between group comparisons of clinical efficacy (i.e., differences between baseline and follow-up) we used the data obtained in the LOCF of each case. The percent of change between baseline and LOCF (positive, negative, general and total PANSS scores) was calculated and compared between clozapine and risperidone treated patients by Mann–Whitney U tests. Additionally, we assessed the significance of changes within each group for positive, negative, general and total PANSS scores between baseline and LOCF by Wilcoxon tests.

Third, we repeated these comparisons in the patients still in treatment after 12 months (i.e., between baseline and 12-month scores). These comparisons were carried out with Mann–Whitney U tests (between-group differences in percent of change), and Wilcoxon tests (within-group changes).

Since side effects of the trial drugs might explain changes in negative symptoms, we investigated if the differences in clinical response. To do so, we defined two scores derived from the UKU: "motor" (M) (sum of severity scores for dystonia, rigidity, hypokinesia, hyperkinesia, tremor and achatysia) and "subjective"

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