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Clinical predictors of therapeutic response to clozapine in a sample of Turkish patients with treatment-resistant schizophrenia

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Abstract

Background: Several lines of evidence suggest that clozapine is more effective than both first- and second-generation antipsychotic drugs in treatment-resistant schizophrenia (TRS). However, clinicians appear to be hesitant to prescribe this drug. It would therefore be extremely valuable if predictors of response to clozapine could be identified. The aim of this study was to evaluate the predictive factors of clinical responses to clozapine in a group of Turkish patients with TRS.
Methods: This was a 16-week uncontrolled open study carried out among 97 TRS patients (80 males and 17 females; DSM-IV diagnosis). All patients fulfilled the criteria for refractory schizophrenia according to the UK guidelines for the National Institute of Clinical Excellence (NICE). After all previous antipsychotic medications had run their course, the patients were started on clozapine according to a standardized titration and dosage schedule. Psychopathology was evaluated before the initiation of clozapine therapy and once every 4 weeks using the Brief Psychiatric Rating Scale (BPRS), the Scale for the Assessment for Positive Symptoms, and the Scale for the Assessment of Negative Symptoms.
Results: Of the TRS patients on clozapine, 55.7% achieved a clinical response, defined as at least a 20% decrease in BPRS. We observed a favorable effect of clozapine on both positive and negative symptoms. Logistic regression analysis showed that a good clozapine response was more likely when schizophrenia began at a later age, when negative symptoms were severe, and when patients had an early response at 4 weeks.
Conclusion: A combination of demographic, baseline clinical, and acute treatment response variables may accurately predict response to clozapine in TRS. Priority should be given to initiating clozapine at the earliest phase of TRS, especially for patients with evident negative symptoms.

Keywords: Clozapine response; Predictor; Treatment-resistant schizophrenia

1. Introduction

About 20 to 40% of patients suffering from schizophrenia derive little or no benefit from treatment with conventional or novel atypical antipsychotics (Hellewell, 1999; Conley and Kelly, 2001). Clozapine is now well established as the treatment of choice for severely ill schizophrenic patients who are refractory to treatment. Studies with patients who exhibited inadequate therapeutic responses to conventional antipsychotic drugs have clearly demonstrated that clozapine is more effective than treatment with any other conventional neuroleptic (Kane et al., 1988; Pickar et al., 1992; Breier et al., 1994; Wahlbeck et al., 1999). Recent studies have suggested that clozapine may be superior to other atypical antipsychotics in controlling symptoms that do not respond to conventional drugs in patients with chronic schizophrenia (Chakos et al., 2001; Tuunainen et al., 2001; Volavka et al., 2002; McEvoy et al., 2006). However, approximately 40 to 70% of treatment-resistant schizophrenic

Abbreviations: BPRS, Brief Psychiatric Rating Scale; NICE, National Institute of Clinical Excellence; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment for Positive Symptoms; TRS, treatment-resistant schizophrenia.

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patients are also not responsive to clozapine, as they have persistent positive, negative, or residual symptoms and cognitive deficits despite clozapine monotherapy of adequate dosage and duration (Kane et al., 1988; Meltzer et al., 1990).

Although a substantial number of treatment-resistant schizophrenia (TRS) patients improve when treated with clozapine, clinicians are sometimes hesitant to use this agent because of its side-effects, including agranulocytosis, seizures, and weight gain. One of the most important deterrents to using clozapine in clinics is the lack of predictors of response to clozapine treatment and the current inability to identify patients for whom clozapine treatment should be prioritized. Therefore, it is of special interest to investigate the differences in clinical variables between responders and non-responders to this drug. In recent years, several studies (Marder and Van Putten, 1988; Meltzer et al., 1989; Fenton and Lee, 1993; Lieberman et al., 1994a,b; Pickar et al., 1994; Buchanan et al., 1998; Rosenheck et al., 1998; Umbricht et al., 2002; Meltzer et al., 2003) have investigated possible clinical predictors of responses to clozapine treatment. In these studies, male gender (Lieberman et al., 1994a), earlier (Buchanan et al., 1998) as well as later (Lieberman et al., 1994b; Pickar et al., 1994) age at onset, shorter duration of illness (Lieberman et al., 1994a), higher levels of positive symptoms (Meltzer et al., 1989; Rosenheck et al., 1998; Umbricht et al., 2002), lower levels of negative symptoms (Fenton and Lee, 1993), weight gain (Meltzer et al., 2003), and a paranoid subtype of schizophrenia (Meltzer et al., 1989; Fenton and Lee, 1993; Lieberman et al., 1994a,b) have been reported to predict good responses to clozapine. However, because of inconsistent and somewhat contradictory results, there has been no consensus on these determinants.

Most of the relevant studies have been conducted in European–American populations, and there are few reports (Wong et al., 2006) investigating ethnic differences in responsiveness to clozapine. It would be valuable if predictors of response to clozapine could be identified among different populations. No study to date has reported clinical differences between Turkish schizophrenia patients who respond to clozapine and those who do not. Our aim was to identify the possible clinical predictive factors of a therapeutic response to clozapine in Turkish TRS patients who were assigned to a naturalistic clinical study.

2. Materials and methods

2.1. Subjects

This study was an uncontrolled prospective open study and formed part of a trial assessing genetic determinants of resistant schizophrenia patients treated with clozapine. It was conducted in the Adult Psychiatry Department of the GATA Haydarpasa Veteran Hospital in Istanbul, Turkey. Ninety-seven subjects (80 males, 17 females) were included in the trial; subjects were included if they were between 18 and 60 years of age and fulfilled DSM-IV criteria for schizophrenia established on the basis of SCID-I.

Subjects who received clozapine in this study were treatment-resistant according to the NICE (National Institute of Clinical Excellence) criteria (2002), as evidenced by a lack of satisfactory clinical improvement despite the sequential use of the recommended doses of at least two antipsychotic drugs for 6–8 weeks, at least one of which was a second-generation antipsychotic. Our exclusion criteria were: a diagnosis other than schizophrenia in axis I of the DSM-IV (particularly schizoaffective conditions); low white blood cell counts (less than 3.5×10^9/l); a history of alcohol or drug abuse in the last 2 years; serious medical illness; concomitant medication until the end of the study period; and drug induced agranulocytosis (absolute granulocyte count less than 0.5×10^9/l). The study was approved by the Local Ethics Committee. All patients or their caregivers were informed, and gave consent to take part in the study.

2.2. Procedure

At the beginning of this 16-week open study, demographic data and psychiatric history were recorded, and physical examinations and laboratory investigations were carried out. Doses of antipsychotics that subjects were taking before this study were reduced gradually until they were terminated. After a 1-week drug-free period (6 weeks for depot antipsychotics), clozapine treatment was started at 25 mg in one or two daily doses depending on the patient's tolerance with dose increases in increments of 25 to 50 mg every 3–4 days. The dose was increased to 450 mg daily on the 5th week. No patient received

Table 1
Demographics and clinical variables

Patients' characteristics	Responders ($n=54$)	Non-responders ($n=43$)	Analysis (χ^2 or t)	p value
Gender (male to female ratio)	46/8	34/9	0.6	0.43
Age (years)	31.3±11.0	29.3±9.7	0.9	0.36
Age at onset (years)	25.1±9.5	21.6±5.3	2.3	0.03
Number of hospitalizations (≥3)	17 (31.5%)	17 (39.5%)	0.7	0.41
Subtype of schizophrenia (paranoid)	13 (24.1%)	9 (20.9%)	0.1	0.71
Mean clozapine dosage (mg/day)	294.4±94.0	325.6±87.5	−1.7	0.10
Weight gain at the endpoint (kg)	5.3±3.0	4.8±2.6	0.89	0.38
BPRS score at baseline	58.1±12.4	54.6±12.5	1.4	0.17
SAPS score at baseline	60.8±16.5	59.1±17.5	0.5	0.61
SANS score at baseline	77.4±29.4	59.3±32.7	2.8	0.005
Reduction in BPRS at endpoint	43.0±14.9	13.3±6.0	13.3	<0.001
Reduction in SAPS at endpoint	45.4±20.2	19.5±13.7	7.2	<0.001
Reduction in SANS at endpoint	50.8±30.0	16.6±20.9	6.6	<0.001