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Minocycline add-on to risperidone for treatment of negative symptoms in patients with stable schizophrenia: Randomized double-blind placebo-controlled study

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ABSTRACT

The objective of this study was to assess the efficacy and tolerability of minocycline add-on to risperidone in treatment of negative symptoms of patients with chronic schizophrenia. In a randomized double-blind placebo-controlled study, 40 patients with chronic schizophrenia who were stabilized on risperidone for a minimum duration of eight weeks were recruited. The patients were randomly assigned to minocycline (titrated up to 200 mg/day) or placebo in addition to risperidone (maximum dose of 6 mg/day) for eight weeks. Positive and Negative Syndrome Scale (PANSS), Hamilton Depression Rating Scale, and Extrapyramidal Syndrome Rating Scale were used. Thirty-eight patients completed the study. Significant time × treatment interaction for negative [$F(2.254,85.638)=59.046$, $P<0.001$] general psychopathology [$F(1.703,64.700)=6.819$, $P=0.001$], and positive subscales [$F(1.655,62.878)=5.193$, $P=0.012$] as well as total PANSS scores [$F(1.677,63.720)=28.420$, $P<0.001$] were observed. The strongest predictors for change in negative symptoms were the treatment group ($\beta=-0.94$, $t=-10.59$, $P<0.001$) followed by the change in PANSS positive subscale ($\beta=-0.185$, $t=-2.075$, $P=0.045$). Side effect profiles of the two treatment regimens were not significantly different. Minocycline seems to be an efficacious and tolerable short-term add-on to risperidone for treatment of negative and general psychopathology symptoms of schizophrenia.

1. Introduction

Dopaminergic system imbalance is the most widely studied mechanism in pathophysiology of schizophrenia. Blocking the dopamine receptors by means of current antipsychotics mostly relieves positive symptoms with limited effects on negative or cognitive symptoms (Murphy et al., 2006). Atypical antipsychotics have been reported to be effective in treating negative symptoms although their effect is suboptimal (Murphy et al., 2006). Nevertheless, recent studies do not support the original claims of "atypical antipsychotics having beneficial effects on negative symptoms in schizophrenia" (National Institute for Clinical Excellence, 2009; Leucht et al., 2009). Evidence suggests that in addition to dopaminergic pathways, other neurotransmitter mechanisms including serotoninergic and glutamatergic as well as inflammatory and oxidative pathways might be implicated in the pathophysiology of negative and cognitive symptoms of schizophrenia (Tuominen et al., 2005; Murphy et al., 2006).

Minocycline is a second-generation brain-penetrable tetracycline with antimicrobial and anti-inflammatory effects as well as N-Methyl-D-Aspartate (NMDA) receptor modulating properties (Macdonald et al., 1973; Chaves et al., 2009). Neuroprotective effects of minocycline were first seen in studies on mouse model of Huntington's disease (Berger, 2000) and amyotrophic lateral sclerosis (Zhang et al., 2003) in which minocycline delayed mortality and prevented disease progression. Subsequently, minocycline was shown to be effective in neurological diseases such as Parkinson's disease (Du et al., 2001) and ischemia (Yrjanheikki et al., 1999) in humans. In one case report, several psychiatric

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symptoms of a patient with Huntington's disease were improved by minocycline administration (Denovan-Wright et al., 2002). A study has shown that microglial activation and proliferation and nitric oxide synthesis is inhibited by minocycline (Miyaoka et al., 2008).

Treatment of schizophrenia still remains a challenge. Anti-inflammatory drugs such as celecoxib have been useful in treating symptoms of schizophrenia (Akhondzadeh et al., 2007). NMDA receptor of glutamate has been of increasing interest as a target for treatment of negative and cognitive symptoms of schizophrenia (Rezaei et al., 2013). Several studies have suggested that drugs with action on NMDA receptors might be effective in the treatment of schizophrenia (Rezaei et al., 2013; Farokhnia et al., 2013). A number of studies suggest that minocycline prevents the neurotoxic effects of NMDA antagonists and may exert a differential effect on NMDA receptor signaling pathways (Zhang et al., 2007; Fujita et al., 2008). In one study, administration of minocycline for patients with catatonic schizophrenia showed encouraging results (Ahuja and Carroll, 2007). In an open label study, efficacy of minocycline in schizophrenia was assessed. This study showed that minocycline can be an effective agent for treating schizophrenia (Miyaoka et al., 2008). Two randomized double-blind placebo-controlled clinical trials (RCTs) investigated the effect of minocycline on negative symptoms of early-stage schizophrenia. The results showed that combination of minocycline with a standard treatment of schizophrenia significantly improves the negative symptoms (Levkovitz et al., 2010; Chaudhry et al., 2012). The efficacy of minocycline treatment in patients with chronic stable schizophrenia has not been investigated yet.

We hypothesized that minocycline add-on to risperidone can play a beneficial role in the reduction of primary negative symptoms in patients with chronic schizophrenia. This study assessed the adjunctive effect of minocycline to risperidone as a popular atypical antipsychotic on negative symptoms of patients with stable chronic schizophrenia.

2. Methods

2.1. Trial design and setting

This was an eight-week, double-center, randomized, double-blind, placebo-controlled, parallel-group trial. Each patient was evaluated at baseline visit and at weeks 2, 4, 6, and 8. The study was authorized by the institutional review board of Tehran University of Medical Sciences (TUMS) (Grant no.: 11921), performed in accordance with the Declaration of Helsinki, and approved by the ethics committee at TUMS. Written informed consent was obtained from the eligible participants and their legal representative before entering the study and the patients were informed about their right to withdraw from the study anytime they wish. This trial was registered in the Iranian Clinical Trials Registry (IRCT201202241556N34; www.irct.ir)

2.2. Participants

Male and female outpatients aged 18–50 years were eligible to participate in this study if they had a diagnosis of schizophrenia based on the DSM IV-TR criteria (American Psychiatric Association., 2000) and a minimum disease duration of two years. Diagnosis was based on Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID) and was confirmed with chart review and senior physician interview. Moreover, the eligible patients were required to be treated with a stable dose of risperidone for a minimum of eight weeks and had to be clinically stable for at least four weeks before the study. Clinical stability was defined as $\leq 20\%$ total score change on two consecutive ratings on the positive and negative syndrome scale (PANSS) (Kay et al., 1987). Patients with significant depression, defined as a score ≥ 14 on the 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) or a score of ≥ 4 on depression item of PANSS, were excluded from the study. Other exclusion criteria were serious medical or neurological disorders, any other psychiatric disorder on axis I, alcohol or substance (other than nicotine) dependence, mental retardation (based on clinical judgment), history of hypersensitivity to minocycline, pregnancy, lactation, and hepatic or kidney disease. Women in reproductive age were included only if they were using a reliable contraception method. Patients were also excluded if they had received electroconvulsive therapy (ECT) during the last two weeks. Patients were not allowed to use antidepressants, mood stabilizers, or a second antipsychotic (as an augmentative strategy) during the course of the trial.

2.3. Study settings

The study was conducted in outpatient general psychiatry clinics of Roozbeh psychiatric hospital (Tehran University of Medical Sciences, Tehran, Iran) and Razi Hospital (Welfare Sciences University, Tehran, Iran) from March to October 2012. There were no ethnical or regional restrictions for participants as they were referred from different parts of Tehran and different regions of Iran as long as the patients and their families could adhere to the trial plan.

2.4. Interventions

Eligible patients were randomized into two groups to receive risperidone (Risperdal, Janssen Pharmaceuticals) plus either minocycline or placebo for eight weeks. The dose of risperidone was 4–6 mg/day during the course of the trial. Minocycline initial dosage was 100 mg/day for the first week followed by 200 mg/day for the subsequent seven weeks. Patients did not receive any behavior intervention therapy during the course of the trial.

2.5. Outcomes

The efficacy assessment measure in this study was the PANSS. This is a 30-item rating scale which has been widely used for measuring the severity of symptoms in patients with schizophrenia and has been applied in several studies in Iran (Ghaleiha et al., 2010; Akhondzadeh et al., 2011; Arbabi et al., 2012). It consists of validated subscales to examine positive (7 items), negative (7 items) and general psychopathological (16 items) symptoms of schizophrenia. These three subscales are summed up in the PANSS total score (Kay et al., 1987). Patients were rated by PANSS based on a structured clinical interview at weeks 0, 2, 4, 6, and 8 following the baseline/screening session. In addition, HDRS was administered at baseline and week 8 in order to assess changes in depressive symptoms. This clinician-rated scale contains 17 questions (measured either on 5-point or 3-point scales) which assess the severity of depression-related symptoms (Hamilton, 1960). The difference in the PANSS negative subscale score decrease from baseline to week 8 between the two groups was the primary outcome measure in this study. The difference between the two study groups on the basis of changes in other PANSS subscales and the PANSS total score was considered as secondary outcome measures. Four trained raters were responsible for rating the patients with an inter-reliablity of $>90\%$ on PANSS total symptoms.

2.6. Side effects

Patients were encouraged to inform the research team about any unexpected symptom after entering the study. Side effects were recorded at each visit using a subjective 25-item checklist covering a broad range of complaints. Extrapyramidal Symptoms Rating Scale (ESRS) (part one: parkinsonism, dystonia, dyskinesia; sum of 11 items) (Chouinard and Margolese, 2005) was administered at baseline and week 8 in order to assess the extrapyramidal symptoms. The behavioral and side effects appraisals were completed by independent raters. A thorough physical examination was performed and vital signs were recorded at the screening session and each post-baseline visit.

2.7. Sample size

Assuming a difference of 3 between the two groups of the trial on the PANSS negative subscale, a standard deviation (S.D.) of 3, a two-tailed significance of 0.05, and a power of 80%, a sample size of 32 were calculated (based on our pilot study). Forty patients were planned for recruitment with a 20% drop-out rate assumption.

2.8. Randomization, allocation concealment and blinding

A computer-generated code was used in order to randomly assign the patients to minocycline or placebo group in a 1:1 ratio. The assignments were kept in sequentially numbered sealed, opaque envelopes until the end of the study. The patients and the psychiatrists who referred them were blind to assignments as well as the rater and the person who administered the medications. Different persons were responsible for random allocation and rating of the patients. Placebo was identical in appearance (shape, size, color, and taste) to minocycline and was dispensed by the investigational drug pharmacist.