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Riluzole combination therapy for moderate-to-severe major depressive disorder: A randomized, double-blind, placebo-controlled trial

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ABSTRACT

Recent evidences suggest that glutamatergic dysregulation implicated in neural plasticity and cellular resilience may contribute to the pathophysiology of Major Depressive Disorder (MDD). Riluzole, which exerts its effect by targeting glutamate neurotransmission, has shown antidepressant effect in recent preclinical, observational and open label studies. This study aimed to assess the efficacy and tolerability of riluzole in patients with MDD. Sixty-four inpatients with diagnosis of moderate to severe major depressive disorder participated in a parallel, randomized, controlled trial, and sixty patients underwent 6 weeks treatment with either riluzole (50 mg/bid) plus citalopram (40 mg/day) or placebo plus citalopram (40 mg/day). All participants were inpatients for the whole duration of the study. Patients were assessed using Hamilton depression rating scale (HDRS) at baseline and weeks 2, 4 and 6. The primary outcome measure was to assess the efficacy of riluzole compared to placebo in improving the depressive symptoms. General linear model repeated measures demonstrated significant effect for time × treatment interaction on HDRS [$F(1.86, 107.82) = 8.63$, $p < 0.001$]. Significantly greater improvement was observed in HDRS scores in the riluzole group compared to the placebo group from baseline HDRS score at weeks 2, 4 and 6 ($p < 0.001$, $p = 0.001$, $p = 0.002$, respectively). Significantly greater response with greater speed to treatment was observed in the riluzole group than the placebo group. No serious adverse event occurred. This study showed a favorable safety and efficacy profile in patients with major depressive disorder. Larger controlled studies with longer treatment periods are needed to investigate long term safety, efficacy and optimal dosing.

1. Introduction

Major depressive disorder (MDD) is a chronic, disabling psychiatric disorder associated with high morbidity and mortality throughout the world. The World Health Organization (WHO) points out that unipolar depressive disorders rank third amongst contributors to the global disease burden (Collins et al., 2011).

Although considerable advances in treatment of depression have occurred, several problems still remain. Available treatments are associated with a large number of adverse effects. In addition, substantial proportion of MDD patients do not adequately respond to their first medication and existing treatments are associated with clinically significant lag time to onset of therapeutic efficacy, which is associated with significant morbidity and suicidal risk (Ates-Alagoz and Adejare, 2013; Lapidus et al., 2013; Mathews et al., 2012; Zarate et al., 2010). Resistant patients are usually managed by switching treatment to another medication or augmentation therapy. Recently, there is growing evidence for combination therapy as initial treatment to achieve greater and quicker response. However, studies in support of this notion have not been definitive (Sepanjnia et al., 2012; Shelton et al., 2010).

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Most MDD pathophysiology etiological theories used to focus on brain modulatory monoamine systems (dopamine, serotonin and norepinephrine). A more recent line of evidence points to glutamate, the brain's principal excitatory neurotransmitter, as playing a role in MDD's pathophysiology. Additionally, glutamate dysregulation is known to cause impairments in structural plasticity and cellular resilience, which seems to be implicated in mood disorders as well (Pittenger et al., 2008; Zarate et al., 2003; Zarate and Manji, 2008). It is therefore reasonable to hypothesize that medications which reduce glutamatergic tone may be able to play a role in treatment of depression. One candidate drug is riluzole which has antiepileptic, neuroprotective, and modulatory properties on the glutamatergic neurotransmission. Clinical evidence from several, mostly open label and observational studies, have suggested efficacy of riluzole in treatment of unipolar or bipolar depression and treatment-resistant major depression (Brennan et al., 2010; Sanacora et al., 2004, 2007; Singh et al., 2004; Zarate and Manji, 2008; Zarate et al., 2004, 2005). Riluzole appears to cause no adverse effect on hippocampal plasticity, sparing episodic and visuospatial memory, thus mitigating a theoretical concern regarding its use in the elderly (Sasaki-Hamada et al., 2013).

Based on the available data, we hypothesized that riluzole might be an appropriate augmentative option for improving depressive symptoms, considering its modulatory properties on the glutamatergic neurotransmission and its acceptable safety. Therefore, a randomized, placebo-controlled trial was designed to assess the safety and efficacy of riluzole in combination with citalopram, as a standard of care agent, in improving depressive symptoms in MDD patients. Since our subjects were inpatients, we administrated riluzole and citalopram simultaneously for feasibility of the study process and to decrease the duration of hospitalization. However, in the clinical practice, it would be more practical to consider administration of riluzole in patients who are non-responder or partial responders to standard therapeutic agents.

2. Patients and methods

2.1. Trial design and setting

This 6-week, two-center, randomized, double-blind, placebo-controlled, parallel-group trial was performed between March 2014 and March 2015, in the inpatient clinic of Roozbeh Psychiatric Hospital affiliated with Tehran University of Medical Sciences (TUMS) and Razi Psychiatric Hospital affiliated with the Welfare and Rehabilitation University. The study was approved by the institutional review board (IRB) of TUMS (Grant No: 22192), and was performed consistent with Declaration of Helsinki and its subsequent revisions. Written informed consent was obtained from all eligible participants following complete description of study details. Participants were informed that they were free to withdraw from the trial anytime without any negative effect on their therapy. The trial was registered at the Iranian registry of clinical trials (www.irct.ir; registration number: IRCT201307181556N54).

2.2. Participants

Male and female inpatients between 18 and 50 years of age with diagnosis of major depressive disorder based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) were included in this study as verified by the Structured Clinical Interview for DSM-IV axis-I disorders/patients edition (SCID-I/P). Patients were required to have a score of at least 19 on the 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) and a score of 2 or more on item 1 of HDRS. Citalopram was the drug of choice for patients regardless of other eligibility criteria. Exclusion criteria included: Presence of psychosis, any other mental disorder on DSM-IV axis I (Subjects were excluded if they had another Axis I disorder as a principal diagnosis in the 6 months prior to screening. Comorbid Axis I diagnoses of anxiety disorders were permitted if they were not the primary focus of treatment within 6 months before trial), suicidal ideation (score > 2 on the suicide item of the HDRS, or those who were judged to have substantial risk of suicide by the physician), mental retardation (intelligence quotient < 70 based on clinical judgment and reviewing prior neurocognitive testing and records), any antidepressant use during the last one month or electroconvulsive therapy (ECT) during the last two months, or use of any psychotropic medication during the last three months, alcohol or substance (with the exception of nicotine) dependence, existence of serious or life-threatening medical conditions, presence of hypothyroidism, cardiovascular problems, rising liver transaminases to three times the upper limit of normal or higher, pregnancy and lactation.

2.3. Intervention

Eligible participants were randomly assigned to receive either 50 mg Riluzole bid (Rliutek; Sanofi-Aventis, 50 mg tablet) daily or placebo tablets, in the same manner, for six weeks. All patients, regardless of their assigned group, received 20 mg/day citalopram for the first week and 40 mg/day for the subsequent 5 weeks. Participants were not allowed to undergo any behavioral intervention therapy or use any psychotropic drugs or undergo ECT during the course of the trial.

2.4. Outcome

All participants were evaluated using HDRS at baseline and weeks 2, 4 and 6. HDRS is a validated 17 item (on a three-point or five-point scale) rating scale which evaluates the severity of depressive-related symptoms (Hamilton, 1960). HDRS has been used to assess treatment efficacy and severity of depressive symptoms in several clinical trials in Iran (Abbasi et al., 2015; Emadi-Kouchak et al., 2016; Jafari et al., 2015; Mohammadinejad et al., 2015; Zeinoddini et al., 2014, 2015). Two psychiatrists with previous experience in this field conducted all assessments and the inter-rater reliability (intra-class correlation coefficient) between the two raters was >0.90. The primary outcome measure of this trial was evaluation of riluzole efficacy in improvement of depressive symptoms compared to placebo using general linear model repeated measures. Two groups were also compared with respect to the reduction in HDRS scores from baseline at each time point, early improvement (≥20% reduction in HRDS score within the first two weeks), response to treatment (≥50% reduction in the HDRS score), remission rate (HDRS score ≤ 7) and the time needed to respond to treatment.

2.5. Safety

Patients were asked to immediately inform the research team about any unexpected symptom or complaint during the course of the trial. All patients underwent a thorough physical examination at the screening session and at each visit. All participants were systematically asked for adverse events at each visit through open-ended questioning followed by a complete side effects checklist (a 25-item checklist). Furthermore, complete blood count (CBC) was obtained and serum aminotransferases were measured at baseline and weeks 0, 3 and 6.