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Intravenous Esketamine in Adult Treatment-Resistant Depression: A Double-Blind, Double-Randomization, Placebo-Controlled Study

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ABSTRACT

BACKGROUND: The purpose of this study was to assess the efficacy and safety and to explore the dose response of esketamine intravenous (IV) infusion in patients with treatment-resistant depression (TRD).

METHODS: This multicenter, randomized, placebo-controlled trial was conducted in 30 patients with TRD. Patients were randomly assigned 1:1:1 to receive an IV infusion of .20 mg/kg or .40 mg/kg esketamine or placebo over 40 minutes on day 1. The primary end point was change in Montgomery–Åsberg Depression Rating Scale total score from day 1 (baseline) to day 2. Nonresponders who received placebo on day 1 were randomly assigned again 1:1 to IV esketamine .20 mg/kg or .40 mg/kg on day 4. Secondary efficacy and safety measures were also evaluated.

RESULTS: Of the enrolled patients, 97% (29 of 30) completed the study. The least squares mean changes (SE) from baseline to day 2 in Montgomery–Åsberg Depression Rating Scale total score for the esketamine .20 mg/kg and .40 mg/kg dose groups were −16.8 (3.00) and −16.9 (2.61), respectively, and showed significant improvement (one-sided $p = .001$ for both groups) compared with placebo (−3.8 [2.97]). Esketamine showed a rapid (within 2 hours) and robust antidepressant effect. Treatment-emergent adverse events were dose dependent. The most common treatment-emergent adverse events were headache, nausea, and dissociation; the last-mentioned was transient and did not persist beyond 4 hours from the start of the esketamine infusion.

CONCLUSIONS: A rapid onset of robust antidepressant effects was observed in patients with TRD after a 40-minute IV infusion of either .20 mg/kg or .40 mg/kg of esketamine. The lower dose may allow for better tolerability while maintaining efficacy.

Keywords: Efficacy, Esketamine, Intravenous, Safety, TRD, Treatment-resistant depression

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Major depressive disorder (MDD) is a recurrent and disabling psychiatric illness that is projected to be the leading cause of disease burden worldwide by 2030 (1,2). Nearly one third of patients with MDD do not achieve remission from currently available treatments and are considered to have treatment-resistant depression (TRD), which is associated with chronicity, morbidity, and functional disability (3–6). A significant need exists to develop novel treatments for patients with TRD (7–9).

Ketamine is a racemate that comprises the R-(−)-ketamine enantiomer (arketamine) and the S-(+)-ketamine enantiomer (esketamine). Esketamine has a threefold to fourfold higher affinity for *N*-methyl-D-aspartate (NMDA) receptors than arketamine (10–12). The mechanism of action putatively results from noncompetitive binding to NMDA glutamate receptors. The rapid-onset antidepressant effects associated with ketamine and its reported efficacy in patients with depression who had been unresponsive to conventional antidepressant treatments have generated considerable interest among clinicians and researchers (13–20). In addition, most of the studies conducted previously focused on the safety and efficacy of a single intravenous (IV) ketamine infusion (.5 mg/kg) (14,16,19). However, there is evidence that most patients who respond to ketamine relapse within several days or up to 1 week after a single infusion (14,21,22). It is important to identify a strategy for maintaining the antidepressant effects of ketamine. This proof-of-concept trial evaluates, for the first time, the antidepressant efficacy and safety profile of .20 mg/kg and .40 mg/kg IV esketamine compared with IV placebo in patients with TRD.

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METHODS AND MATERIALS

The protocol and informed consent documents were approved by independent ethics committees or institutional review boards. Written informed consent was obtained from all participants at screening.

Participants

Participants included men and women 18–64 years old who met DSM-IV-TR (23) diagnostic criteria for recurrent MDD without psychotic features, based on clinical assessment and confirmed by the Mini-International Neuropsychiatric Interview (24). Based on the conventional definition of TRD (25), patients were required to have had an inadequate response to at least one antidepressant drug in their current depressive episode and an inadequate response to at least one other antidepressant either in their current or in a previous depressive episode, as assessed by the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (4). At screening and on day −1, patients were also required to have a total score of at least 34 on the Inventory of Depressive Symptomatology–Clinician Rated, 30-Item (mild, 12–23; moderate, 24–36; severe, 37–46; very severe, 47–84) (26). Exclusion criteria included any primary DSM-IV-TR diagnosis of active generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, posttraumatic stress disorder, anorexia nervosa, or bulimia nervosa; patients were also excluded if they had been acutely suicidal or homicidal requiring hospitalization in the past 12 months or had a history of previous nonresponse to ketamine or esketamine.

Study Design

This double-blind (DB), double-randomization, placebo-controlled, multicenter study comprised three phases: screening (up to 2 weeks), DB treatment (day 1 to day 7), and posttreatment (4 weeks, comprising an optional open-label phase lasting up to 2 weeks and a follow-up phase making up the remainder). On day 1 (first dose) of the DB treatment phase, patients were randomly assigned 1:1:1 to receive an IV infusion of .20 mg/kg or .40 mg/kg esketamine or placebo (.9% saline solution) over 40 minutes. All patients received the study medication by continuous infusion using an electronic infusion pump, which was managed by an anesthesiologist or other physician experienced with ventilation management in each clinical site. Responders after the single dose were defined as patients experiencing a reduction of >50% in the Montgomery–Åsberg Depression Rating Scale (MADRS) (27) total score on days 2, 3, or 4 (before the second dose) versus day 1 (baseline). On day 4 (second dose) of the DB treatment phase, responders received the same treatment as day 1. For nonresponders, the following rules were applied: 1) patients who received placebo on day 1 were randomly assigned again 1:1 to IV esketamine .20 mg/kg or .40 mg/kg, and 2) patients who received esketamine .20 mg/kg or .40 mg/kg on day 1 received esketamine .40 mg/kg on day 4.

For both randomizations (on day 1 and day 4), central randomization was implemented based on a computer-generated randomization schedule prepared by the sponsor before the study. The randomization was balanced by using randomly permuted blocks and was stratified by study center. On day −1 or day 1 before dosing, the unblinded pharmacist at each study site contacted the randomization center and provided the required subject information. The randomization center assigned a randomization number to the subject and informed the unblinded pharmacist at the site about the assigned treatment. On day 3 or day 4 (before the second dose), the investigator informed the unblinded pharmacist whether the subject was a responder or not. To maintain study blinding, the pharmacist contacted the randomization center for each subject (responders and nonresponders) to obtain a new randomization number. During the study, the subject was assessed by qualified trained site raters who were blinded to the subject's treatment. After completing the DB treatment phase, patients—with clinical input from the physician investigators—could choose to receive up to four optional open-label treatments of IV esketamine .40 mg/kg (or lower) on days 7, 10, 14, and 17. Per protocol, if IV esketamine was not well tolerated on day 1 or day 4, the dose for the open-label treatment could start at .30 mg/kg.

Outcome Measures

The primary end point was change in MADRS total score from day 1 (baseline) to day 2 (24 hours after the first infusion). The typical recall period for the MADRS is 7 days, although the MADRS was also administered for a recall period of 2 hours, 4 hours, 24 hours, and since last assessment. For the 2-hour and 4-hour recall periods, the sleep and appetite items were not assessed. Predose scores for these two items obtained on the same day were carried forward unchanged.

Secondary end points included 1) change in MADRS total score from day 1 (baseline) to day 3 and day 4 (before the second dose) and from day 4 (before the second dose) to day 7; 2) change in MADRS total score from day 1 (baseline) to day 35 (including days 7, 10, 14, 17, 21, 28, and 35); 3) proportion of responders after the single dose on days 2, 3, or 4 compared with placebo; 4) change in the Quick Inventory of Depressive Symptomatology–Self Report, 16-Item score from day 1 (baseline) to day 14; and 5) change from day 1 (baseline) to day 7 on Clinical Global Impression–Severity, Clinical Global Impression–Improvement, Patient Global Impression of Severity, and Patient Global Impression of Change.

Safety assessments included treatment-emergent adverse events (TEAEs), clinical laboratory tests, 12-lead electrocardiogram, vital signs, physical examinations, Columbia Suicide Severity Rating Scale (C-SSRS), Clinician Administered Dissociative States Scale (CADSS), Brief Psychiatric Rating Scale (BPRS), and Massachusetts General Hospital-Cognitive and Physical Functioning Questionnaire (MGH-CPFQ). All TEAEs were followed to satisfactory resolution or to a clinically stable end point.

Statistical Analyses

Between each esketamine group and placebo, a planned sample size of 10 per treatment group was estimated to provide 90% power to detect 1) a difference of 60% in response rate (one-sided Fisher's exact test, .10 significance level), assuming a 20% placebo response rate, and 2) a