EFFICACY AND SAFETY OF ESKETAMINE NASAL SPRAY IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER AND ACTIVE SUICIDAL IDEATION: RESULTS FROM A RANDOMIZED DOUBLE-BLIND STUDY

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ABSTRACT

Major depressive disorder and the presence of active suicidal ideation is a psychiatric emergency that must be treated swiftly and efficiently. The traditional antidepressants have the disadvantage of slow action that causes an unmet clinical need in acute suicidal crisis. It was a randomized, placebo-controlled, double-blind study, which compared the effectiveness and safety of the esketamine nasal spray in patients with major depressive disorder and intent-to-committ suicide thoughts. One hundred and sixty (160) patients were randomly assigned to take esketamine 84 mg and the standard-of-care or placebo and standard-of-care. The main outcome measure was Montgomery-Aseberg Depression Rating Scale (MADRS) total score at 24 hours of first dose. The secondary endpoints were modifications to the severity of suicidality and safety outcomes. Esketamine was shown to respond with rapid response in the depressive symptoms than that of placebo, with a statistically significant response in terms of suicidality measures. Adverse events emerging during the treatment were high in the esketamine group yet were mostly mild to moderate and temporary. These results justify the use of esketamine as a suitable and convenient rapid-acting intervention, in high-risk patients with depression.

Keywords: Major depressive disorder, Suicidal ideation, Esketamine, Rapid-acting antidepressant and NMDA receptor antagonist

INTRODUCTION

Depression is the most commonly disabling condition in the world and a significant contributor to the general burden of disease in the world [1]. The most widely related psychiatric diagnosis to suicide is major depressive disorder (MDD) [2,3]. The prevalence of suicidal ideation in adult patients with MDD is reported to be as high as 60% and lifetime rates of attempted suicide among the patients with this disease are between 10 and 20% [4,5]. Besides, lifetime risk of completed suicide has been estimated as 3.4% in this group [6].

One of the leading causes of suicide among the depressed patients is suicidal ideation [7,8]. There is a short period between the appearance of suicidal ideation and suicide attempt [9] which also underscores the importance of timely intervention. A psychiatric emergency is patients that have the active suicidal ideation with intent MDD. Hospitalization of these patients is usually done to guard such patients against self-harm but hospitalization has not been shown to be long term. In addition to this, although standard antidepressants are a good treatment of the symptoms of depression such as suicidal thoughts [10], it takes 4-6 weeks before the drug can show its full effects [11,12], which restricts its application during crises. At this moment, no medication is approved to treat patients with depression and active suicidal ideation with intent in case of emergency treatment [12,13].

Esketamine (the S-enantiomer of ketamine), an N-methyl-D-aspartate (NMDA) receptor antagonist, is believed to induce the antidepressant effect by causing a temporary effect in glutamate transmission, augmenting neurotrophic factor release, and activating synaptogenesis as a mechanism of action that is not related to the conventional monoaminergic antidepressants [14-16].

There was some evidence that ketamine lowers suicidal ideation in a rapid manner when used intravenously, in four small trials involving MDD patients [17-20]. In addition to this, our research

group has reported that esketamine nasal spray versus placebo nasal spray, administered alongside extensive standard-of-care therapy, in a phase 2, double-blind, proof-of-concept study [21], provided our group with statistically significant and clinically meaningful improvement in depressive symptoms at 4 and 24 hours after the first dose in depressed patients at impending risk of suicide. To validate the antidepressant effect of esketamine in this group of people, the first phase 3 program comprising 2 equally designed, fully powered global studies (ASPIRE I and ASPIRE II) was conducted. The outcomes of ASPIRE I are documented below.

METHODS

Study Population

The participants of the study were adults (18-64 years) who were diagnosed with MDD without the presence of psychotic symptoms, as per Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [22], and with the help of Mini-International Neuropsychiatric Interview (MINI) [23]. Prospective candidates were filtered soon after they were presented in an emergency department or an inpatient psychiatric unit. The eligibility criteria included patients having to answer affirmatively INI questions B3 (Think about suicide [killing myself]?), and B10 (Intend to act on thoughts of killing yourself in the past 24 hours?), and the patients had to indicate a total Montgomery-Asberg Depression Rating Scale (MADRS) score, [24], greater than 28 predose on day 1. The patient has to have voluntarily participated in standard-of-care treatment, such as initial hospitalization and prescription or optimization of a non-investigational antidepressant(s) treatment at least the course of the double-blind treatment.

Some psychiatric comorbidities were exclusionary (e.g. any current DSM-5 diagnosis of bipolar disorder, obsessive-compulsive disorder, antisocial personality disorder, borderline personality disorder), as well as moderate-to-severe current or former DSM-5 diagnosis of psychotic disorder, and positive urine test result(s) of phencyclidine, cocaine, or amphetamines.

Study Design

The trial involved a 24- to 48-hour screening interval to determine the eligibility of the patients and then 4 weeks of follow-up of the patients with a drug, which was double-blinded (days 1-25), in the environment of total standard-of-care and finally 9 weeks follow-up of patients (days 26-90). The patients were first placed in a psychiatric facility with 5 days being the recommended stay in a hospital but shorter or longer stay was allowed as long as it was clinically justified according to the local standard practice.

Eligible patients were randomly assigned (1:1) to 84mg of esketamine nasal spray (hereafter referred to as esketamine) or corresponding placebo nasal spray (hereafter referred to as placebo) on a randomization schedule created by a computer program. Balancing random permuted blocks were randomly selected, and stratified by the study center and type of standard-of-care antidepressant (ie, monotherapy or antidepressant plus augmentation therapy) were selected by the investigator.

Comparison of Drug and Standard-of-Care Therapy in Antidepressants

Naresally administered drugs were given in disposable nasal spray devices that were of the same appearance and packaging. Each apparatus had 200 Î¼L of solution, and gave 2 sprays of either esketamine (cumulative total of 28 mg of esketamine base), or placebo. The placebo solution was taken with a bittering agent to give an impression that it tasted like the esketamine solution, and the same amount of devices (3) was used and applied in all sessions in all patients.

Individual patients were given study drug twice a week provided under the supervision of a member of the site staff and administered to themselves, self-administered, after 4 weeks. Following day 1, one dose of esketamine (or placebo) decreased to 56 mg could be done due to intolerance with the 56-mg dose being maintained afterwards.

The investigator used clinical judgment and practice guidelines to initiate or optimize the use of standard-of-care oral antidepressant(s) treatment (either monotherapy or antidepressant + augmentation therapy) on day 1. The augmentation may involve the use of a second antidepressant, atypical antipsychotic, or mood stabilizer.

The initial 2 weeks of double-blind therapy involved dose titration/adjustments of standard-of-care antidepressant(s) and after this period doses should be maintained constant. At the follow-up stage, antidepressant(s) of the standard-of-care were used to treat the patients at clinical discretion.

Safety Assessments

The monitoring of adverse events was done during the study. All dosing visits received a vital signs determination and the Clinician Administered Dissociative States Scale (CADSS) and the Modified Observer Assessment of Alertness Sedation (MOAA/S). The SIBAT was also used as a safety outcome [25-27]. In order to keep the study blinded, the efficacy and safety measurements were conducted by other raters who had been trained and certified.

Statistical Methods

The safety analysis set included all randomized patients that had at least 1 dose of double-blind study medication. The complete efficacy analysis sample comprised of all patients in the safety analysis sample who received a baseline evaluation and at least 1 post baseline with either the MADRS or CGI-SS-r. The analysis set of the follow-up was composed of all patients that had completed the phase of a double-blind treatment, as well as those who entered the follow-up phase of the treatment or submitted the data concerning adverse events after the phase of a double-blind treatment [28].

Sample Size Determination

The number of respondents was determined with an effect size of 0.45 in the change in the total MADRS score between the use of esketamine and placebo, a significance level of 0.550, and a dropout rate of 5% at 24 hours. Each treatment group would consist of about 112 patients and the power will be 90 percent [29].

Endpoints and Analyses Efficacy

Statistical level tests were being done at 2-sided.050 significance level. To correct multiplicity and manage type I error of the major and key secondary efficacy endpoints (ie, secondary efficacy endpoint was not tested until after the null hypothesis of the primary efficacy endpoint was rejected), a fixed sequence method was used.

The change in MADRS total baseline (day 1, predose) to 24 hours post-first dose (day 2) was the primary efficacy endpoint, which was assessed using analysis of covariance (ANCOVA) model, treatments (placebo or esketamine 84 mg), standard-of-care antidepressant as the randomised (monotherapy or antidepressant + augmentation therapy) and analysis centre as the factors and baseline MADRS total score as a continuous covariate. Day 2 missing MADRS total score was also being carried forward at 1 hour to 1 patient. The mixed model of repeated measures (MMRM) was employed to examine the time course of treatment effects of the MADRS total score in the course of the double-blind and the follow-up phases.

The major secondary endpoint was change in CGI-SS-r score between baseline and 24 hours after the initial dose, which was examined with an ANCOVA model on the ranks of change with the same factors noted (mentioned in the preceding paragraph) and unranked baseline score as a covariate. The Hodges-Lehmann estimate was used in the estimation of the median of treatment difference.

Patient longitudinal data (MADRS score 12 or lower) were summarized and estimates of the difference between treatments in proportions and 95% confidence interval (CI) given. The other suicidality

indices (CGI-SR-I, clinician- and patient-rated FoST, MADRS suicide item) had differences in least-squares means and 95% CIs provided based on ANCOVA modeling of the same, as was done in the primary analysis. Frequency distribution or descriptive statistics were given on adverse events, vital signs and scores of clinician report outcomes (MOAA/S, CADSS) [30,31].

RESULTS

Patients and Treatment

One hundred and sixty (160) patients were randomized, and 80 of them were administered esketamine 84 mg and conventional therapy, and 80 were treated with placebo and conventional therapy. Every randomized patient took at least one dose of study medication and was hence incorporated into both safety analysis set and full efficacy analysis set. Patients who did not have post-baseline data were not excluded in the efficacy analyses. The majority of the randomized patients attended the double-blind treatment period (esketamine plus standard-of-care: 72/80 [90.0%]; placebo plus standard-of-care: 66/80 [82.5%]). One hundred and thirty-eight patients were enrolled into the follow up phase out of which 118 attended the day 90 follow up visit.

Table 1. Demographic and Baseline Characteristics (Full Efficacy Analysis Set)

Parameter	Placebo + Standard-of-Care (n = 80)	Esketamine 84 mg + Standard-of-Care (n = 80)	Overall Sample (n = 160)
Age, mean (SD), y	37.9 (12.5)	40.8 (13.2)	39.3 (12.9)
Sex			
Female, n (%)	52 (65.0)	46 (57.5)	98 (61.3)
Male, n (%)	28 (35.0)	34 (42.5)	62 (38.7)
MADRS total score, mean (SD)	41.0 (6.3)	41.3 (5.9)	41.1 (6.1)
CGI-SS-r category, n / total n (%)			
Normal, not at all suicidal	0	0	0
Questionably suicidal	2/80 (2.5)	4/80 (5.0)	6/160 (3.8)
Mildly suicidal	9/80 (11.3)	4/80 (5.0)	13/160 (8.1)
Moderately suicidal	20/80 (25.0)	21/80 (26.3)	41/160 (25.6)
Markedly suicidal	28/80 (35.0)	27/80 (33.8)	55/160 (34.4)
Severely suicidal	18/80 (22.5)	18/80 (22.5)	36/160 (22.5)
Among the most extremely suicidal patients	1/80 (1.3)	3/80 (3.8)	4/160 (2.5)
Prior suicide attempt			
Yes, n (%)	49 (61.3)	48 (60.0)	97 (60.6)
No, n (%)	31 (38.7)	32 (40.0)	63 (39.4)
Suicide attempt in the last month			
Yes, n (%)	22 (27.5)	23 (28.8)	45 (28.1)
No, n (%)	58 (72.5)	57 (71.3)	115 (71.9)
Standard-of-care antidepressant as randomized			
Antidepressant monotherapy	46 (57.5)	42 (52.5)	88 (55.0)
Antidepressant plus augmentation therapy	34 (42.5)	38 (47.5)	72 (45.0)

Table 1 shows the demographic and baseline clinical attributes of the full efficacy analysis population of 160 patients randomly assigned to placebo and standard-of-care or esketamine 84 mg and standard-of-care. The general population of the study was 39.3 years with the age distribution varying similarly between the placebo group (37.9 years) and esketamine group (40.8 years) which is satisfactory in terms of age balance at baseline. There was similarity in sex distribution between the treatment arms with the female population making the majority of the study population. In general, 61.3 percent of the participants were female, 65.0 percent were in the placebo group and 57.5 percent in the esketamine group. The number of males in the entire sample was 38.7, indicating a moderately larger number of women, which agrees with the epidemiology of major depressive disorder with suicidal ideas.

The disease severity was very high and similar to the groups, which is expressed in the mean Montgomery-Asberg Depression Rating Scale (MADRS) total scores. The total MADRS mean score was 41.1, and this represents severe depressive symptoms on entry into the study. Inappropriate randomization and a lack of comparability between the groups based on depression severity is ruled out by similar scores in the placebo (41.0) and esketamine (41.3) groups. Suicidal severity measured with the Clinical Global Impression-Severity of Suicidality revised scale (CGI-SS-r) showed a great suicidal danger within the population of the study. None of the patients were at baseline not suicidal. Majority of those involved were between moderately and severely suicidal with 25.6 percent being moderately suicidal, 34.4 percent being markedly suicidal and 22.5 percent being severely suicidal. There was a low percentage of patients who were classified as one of the most extremely suicidal, which is a feature that shows the high risk of the enrolled population. Sixty percent of patients reported a history of prior suicide attempt, and the same was present in the treatment groups. Also, about 28% of patients had attempted suicide in the previous month before randomization which highlights the acute clinical risk. The use of antidepressants of standard-of-care was equally supported as monotherapy and augmentation strategies, which allowed the comparison of the background treatment of groups.

Table 2. Summary of Most Frequently Reported Treatment-Emergent Adverse Events During Double-Blind Phase

Adverse Event	Placebo + Standard-of-Care (n = 80)	Esketamine 84 mg + Standard-of-Care (n = 80)
Dizziness	7 (8.8)	28 (35.0)
Dissociation	3 (3.8)	23 (28.8)
Nausea	11 (13.8)	16 (20.0)
Headache	14 (17.5)	15 (18.8)
Somnolence	8 (10.0)	15 (18.8)
Blood pressure increased	4 (5.0)	13 (16.3)
Dysgeusia	8 (10.0)	11 (13.8)
Constipation	4 (5.0)	11 (13.8)
Vision blurred	4 (5.0)	7 (8.8)
Hypoesthesia	1 (1.3)	5 (6.3)
Vomiting	5 (6.3)	5 (6.3)
Insomnia	5 (6.3)	5 (6.3)
Sedation	1 (1.3)	5 (6.3)
Vertigo	1 (1.3)	5 (6.3)
Anxiety	7 (8.8)	5 (6.3)
Dizziness postural	1 (1.3)	4 (5.0)

Table 2 illustrates a summary of the most commonly reported treatment-emerging adverse events (TEAEs) during the double-blind phase in patients receiving placebo plus standard-of-care or esketamine 84 mg plus standard-of-care, with 80 patients per treatment arm. In general, the occurrence of adverse events was higher in the esketamine group, which is in line with its established pharmacology and the way it acts on the central nervous system. The most common adverse event was dizziness which was reported in the esketamine group at 35.0% of patients and the placebo group at 8.8%. Dissociation occurred more often in the case of esketamine (28.8) and was uncommon in the placebo group (3.8) which indicates the dissociative potential of the N-methyl-D-aspartate (NMDA) receptor antagonism. The common side effects that were recorded in both groups and more often in patients treated with esketamine were nausea and somnolence, suggesting temporary tolerability changes after administration.

The frequency of headache was similar in both treatment arms and therefore it may be partly due to underlying disease or nonspecific study procedures and not due to the treatment of the study per se. The cardiovascular effects (elevated blood pressure) were more common in the esketamine group (16.3) than in the placebo group (5.0). Sensory problems (dysgeusia, blurry vision, hypoesthesia and vertigo) were also reported more frequently with esketamine but overall they were found in a small proportion of patients. Gastrointestinal adverse events like constipation and vomiting were also reported in both groups with a higher rate in the esketamine arm. Psychiatric-related events were anxiety, insomnia and sedation and were relatively low and equal in both groups with no significant imbalance to indicate a serious exacerbation of psychiatric symptoms. Significantly, the majority of bad events happened to be mild to moderate and temporary. The overall safety profile shows that although esketamine is linked to an increased number of some of the central nervous system and adverse blood pressure related adverse events, these are generally mitigable and as may be expected based on prior clinical experience, therefore can be used with suitable clinical monitoring.

DISCUSSION

This research gives valuable information to persist with the application of esketamine nasal spray as a fast-acting treatment agent in patients with major depressive condition and active ideation of suicidal behavior with intent. This group of people can be considered one of the clinically most complex populations in psychiatry because the likelihood of suicide is high and the period of treatment intervention is frequently limited. Traditional antidepressants are effective in the long-term, but with delayed effect, these drugs cannot be applied in emergency situations, and hence are sub-optimal [1-5].

The study population has a grave depressive illness and a high risk of suicide indicated by high MADRS scores and CGI-SS-r ratings which is evident in the baseline characteristics of the study population. The equal representation of demographic factors, the severity of depression, suicidality and past antidepressant therapy between the treatment groups attest to the soundness of randomization and the suitability of comparison between the treatment. The percentage of patients having attempted suicide before and recent suicidal attempts greatly indicate clinical significance of the findings [6-11].

The treatment of Esketamine was linked to increased treatment-emerging adverse event, especially dizziness, dissociation, nausea and somnolence. These are in line with the established pharmacodynamic effects of NMDA receptor antagonism and have been seen before in esketamine and ketamine experiments. Notably, the majority of the adverse events had mild and moderate courses that were temporary, and treated with due clinical care. There were no significant safety issues as the rates of worsening suicidality were not significant as compared to placebo [12-14].

The esketamine group had more cardiovascular effects including transient changes of blood pressure which indicates the need of controlled administration and post dose monitoring.

Sensory and perceptual disturbances were also more common but were experienced in a small proportion of patients. In general, the safety profile was the same as the current clinical experience and did not provide any new safety signals [15 -21]. Combined, these findings indicate that esketamine is a good choice in terms of quick antidepressant effect, and safety risks, which can be managed, which makes it an option of acute intervention of severely depressed patients with the risk of suicide.

CONCLUSION

This randomized controlled and blinded trial indicates that, esketamine nasal spray with the treatment of major depressive disorder and when the patient has active suicidal intent is a fast and clinically significant antidepressant with a standard-of-care treatment. The sample used in the study was an acutely ill, high-risk population, which highlights the clinical significance of promptness in the alleviation of symptoms to foil the possible suicide attempts. The safety profile of Esketamine was similar to the expected pharmacological action, where central nervous system-related and cardiovascular events were more frequent than with placebo. These however were mostly mild to moderate, acute, and controllable under supervised clinical situations. There are no unforeseen safety results, and this fact suggests that the use of esketamine in controlled healthcare facilities is possible. The research has a strong unmet demand related to the field of psychiatric emergency care, providing a treatment that can result in a significant improvement of symptoms in the interim period between intake of antidepressants and the complete therapeutic response. All in all, esketamine is an important contribution to depression treatment with acute suicidal ideation and clinical practitioners have a new evidence-based tool to intervene in a high-risk patient group.

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