Brain Stimulation 16 (2023) 1041–1043

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.journals.elsevier.com/brain-stimulation

Comparing fast-acting interventions for treatment-resistant depression: An explorative study of accelerated HF-rTMS *versus* intranasal esketamine

Dear Editor,

Treatment-resistant depression (TRD), the non-response to two different antidepressant classes during a major depressive episode, is a severe clinical condition in almost 30% of depressed patients, carrying substantial direct and indirect financial burdens on the healthcare system [1]. Accelerated rTMS (arTMS) protocols are novel approaches that exert a comparable antidepressant efficacy without significantly compromising the safety and tolerability associated with the standard rTMS regimen [2,3]. arTMS also ensures the potential for rapid antidepressant action, observable within the initial post-treatment weeks [4]. This qualifies arTMS as a rapid therapeutic intervention for TRD, comparable to glutamatergic modulators like intranasal esketamine (ESK-NS), an N-methyl-D-aspartate (NMDA) receptor antagonist [5], approved as the first therapeutic agent for TRD by FDA and EMA [6].

A direct comparison between these two treatment protocols is currently missing. Hence, this study aimed to compare (a) the effectiveness and the speed of antidepressant action and (b) the safety and tolerability of arTMS and ESK-NS in treating TRD.

In a multicentric, observational, retrospective study, we studied 59 patients with TRD (women/men, n = 32/n = 27; age, 54.61 ± 11.32) who consecutively underwent either a one-week, high-frequency rTMS protocol (ReModula: four daily sessions of HF-rTMS over the left DLPFC for five consecutive days) or a three-month ESK-NS therapy (biweekly administrations in the first month; weekly in the second month: bimonthly in the third month). Study design and administration procedures of arTMS and ESK-NS are fully detailed in supplementary materials. Treatment assignment (arTMS: n = 30; ESK-NS: n = 29) was determined based on the clinician's judgment. The depression severity was assessed with the total score of the Montgomery–Åsberg Depression Rating Scale (MADRS) at baseline (T0), one month (T1), and three months (T2) after the initiation of treatment.

Sociodemographic and clinical characteristics did not differ between treatment groups at T0 (see supplementary materials), except for a longer duration of the current episode among those patients treated with arTMS (months, 19.57 ± 13.42 *vs.* 12.03 ± 9.47; $t_{57} = 2.484$, p = 0.016).

rm-ANCOVA (within-factor: "time"; between-factors: "gender", "protocol"; covariate: age, duration of the current episode, number of failed antidepressant trials in the current episode) showed a significant "time" × "protocol" interaction effect ($F_{2,104} = 3.814$, p = 0.025, $\eta_p^2 = 0.068$) on MADRS score, with Mauchly's test of sphericity not significant (W = 0.893, $\chi_2^2 = 5.794$, p = 0.055). As shown in Fig. 1A, the MADRS scores between the two groups:

a) did not differ at baseline (p = 0.307);
b) decreased significantly and separately at T1 (arTMS, T0 *vs.* T1: p < 0.001, $d = 1.709$; ESK-NS, T0 *vs.* T1: p < 0.001, $d = 1.361$) and T2 (arTMS, T0 *vs.* T2: p < 0.001, $d = 1.822$; arTMS, T1 *vs.* T2: p = 0.989, $d = 0.218$; ESK-NS, T0 *vs.* T2: p < 0.001, $d = 2.338$; ESK-NS, T1 *vs.* T2: p < 0.001, $d = 1.042$);
c) significantly differed at T1 (p = 0.048), with a higher MADRS decrease ($d = 0.864$) in the arTMS group, but did not at T2 (p = 1.000).

As shown in the upper panels of Fig. 1B, the response rates (RRs) (≥50% decrease of MADRS total score) were significantly higher in arTMS than ESK-NS at T1 (respectively, n = 15/50% *vs.* n = 5/17.24%: $\chi_1^2 = 7.062$, p = 0.008), but not at T2 (n = 18/60% *vs.* n = 20/68.97%: $\chi_1^2 = 0.517$, p = 0.472). The remission rates (MADRS total score <10) did not differ between groups at T1 and T2 (T1, n = 5/16.67% *vs.* n = 1/3.45%: $\chi_1^2 = 2.820$, p = 0.093; T2, n = 12/40% *vs.* n = 10/34.48%: $\chi_1^2 = 0.192$, p = 0.661), as depicted in lower panels of Fig. 1B.

Regarding safety and tolerability, eight patients (26.66%) from the arTMS group and 24 (82.75%) from the ESK-NS group reported treatment-related side effects (trSEs). The most frequent arTMS trSEs were transient post-stimulation headache (13.33%) and scalp discomfort at the stimulation site (10%). Additionally, one participant encountered a mid-episode of agitation throughout the stimulation session, which was transient and didn't require any specific intervention. The most prevalent ESK-NS trSEs were: temporary sedation (55.17%), transient dissociative symptoms (34.5%), short-lived hypertension (10%), and brief agitation (6.89%).

Our findings revealed that arTMS had a more rapid effect, yielding higher RRs at the one-month follow-up than ESK-NS. arTMS accelerated response aligns with previous research, suggesting that faster protocols can shorten treatment duration, maintaining comparable efficacy [2]. Simultaneously, they potentially lead to a swifter response than standard protocols [4]. Besides, the RRs for arTMS and ESK-NS were consistent with existing literature, which reports three-month RRs of 60% for arTMS and 62.06% for ESK-NS among patients with TRD [6,7]. In terms of safety and tolerability, both treatments were found to be safe, with minor and transient trSEs. Notably, arTMS demonstrate lower trSEs incidence, potentially offering a more tolerable treatment option. However, the incidence of ESK-NS trSEs is consistent with real-world settings [6]. Interestingly, neither treatment induced manic switches, confirming their safety [6,8,9].

Several limitations should be considered. Firstly, the retrospective and naturalistic nature of the study did not allow for treatment randomization or the use of blinded assessors. However, the study's design is also a strength since it is more representative of real-world conditions, unlike RCTs which often involve only pre-screened

https://doi.org/10.1016/j.brs.2023.06.003
Received 1 June 2023; Accepted 10 June 2023
Available online 17 June 2023

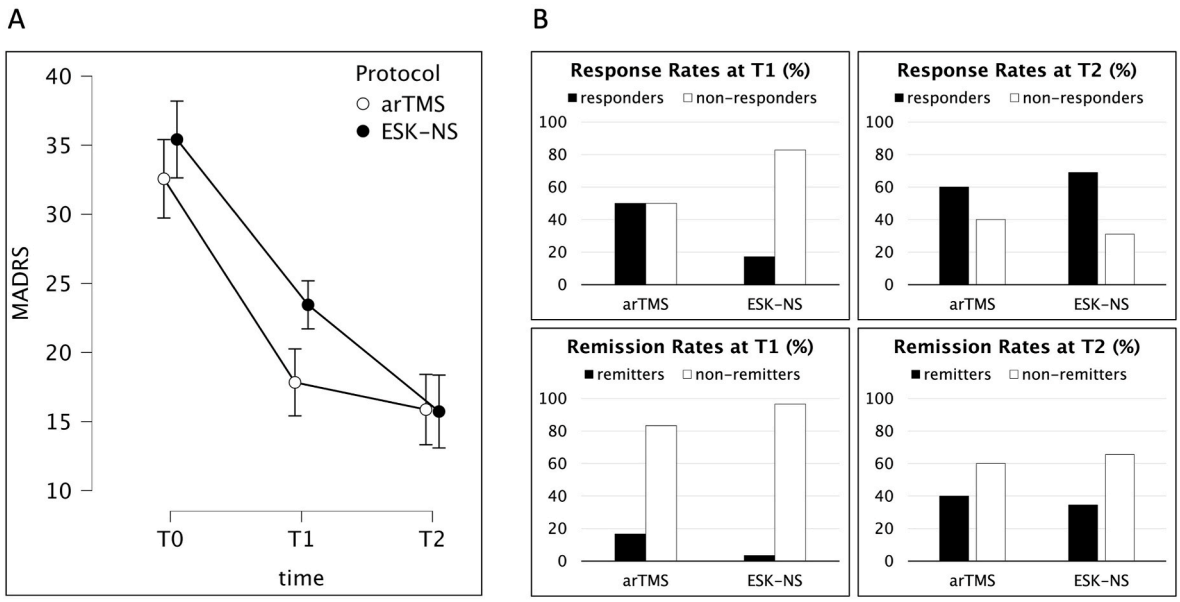

Fig. 1. (A) Means (circles) and 95% confidence intervals (vertical bars) of Montgomery–Åsberg Depression Rating Scale (MADRS) scores in the accelerated rTMS (arTMS) and intranasal esketamine (ESK-NS) protocol groups at baseline (T0), after one month (T1), and after three months (T2) from the treatment beginning. (B) Percentages of the response rates (≥50% decrease of MADRS total score) at T1 (left upper panel) and T2 (right upper panel) and remission rates (MADRS total score <10) at T1 (left lower panel) and T2 (right lower panel) in the arTMS and ESK-NS protocol groups.

subjects. Secondly, the limited sample size of both treatment groups highlights the need for more extensive cohort studies for validation.

The findings from this explorative research should be replicated, especially through randomized prospective studies.

Funding/support

This work was supported by the "Ricerca Finalizzata, Young Researchers Grant" Italian Ministry of Health, Italy, and the "Departments of Excellence 2018–2022" initiative of the Italian Ministry of Education, University and Research.

Declaration of competing interest

Giovanni Martinotti has been a consultant and/or a speaker and/or has received research grants from Angelini, Doc Generici, Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Servier, and Recordati.

Bernardo Dell'Osso has received lecture honoraria from Angelini, Lundbeck, Janssen, Pfizer, Neuraxpharm, Arcapharma, and Livanova.

Giorgio Di Lorenzo has been a speaker and/or a consultant for Angelini, FB-Health, Janssen-Cilag, Livanova, Lundbeck, Neuraxpharm, Otsuka, and Recordati.

The remaining authors declare that the research was conducted without any commercial or financial relationship that could be construed as a potential conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2023.06.003.

References

[1] Zhdanava M, et al. The prevalence and national burden of treatment-resistant depression and major depressive disorder in the United States. J Clin Psychiatry Mar. 2021;82(2). https://doi.org/10.4088/JCP.20m13699.

[2] Sonmez AI, et al. Accelerated TMS for Depression: a systematic review and meta-analysis. Psychiatr Res Mar. 2019;273:770–81. https://doi.org/10.1016/j.psychres.2018.12.041.

[3] Fitzgerald PB, Hoy KE, Elliot D, Susan McQueen RN, Wambeek LE, Daskalakis ZJ. Accelerated repetitive transcranial magnetic stimulation in the treatment of depression. Neuropsychopharmacology Jun. 2018;43(7):1565–72. https://doi.org/10.1038/s41386-018-0009-9.

[4] Cole EJ, et al. Stanford accelerated intelligent neuromodulation therapy for treatment-resistant depression. Am J Psychiatr Aug. 2020;177(8):716–26. https://doi.org/10.1176/appi.ajp.2019.19070720.

[5] d'Andrea G, Pettorruso M, Di Lorenzo G, Mancusi G, McIntyre RS, Martinotti G. Rethinking ketamine and esketamine action: are they antidepressants with mood-stabilizing properties? Eur Neuropsychopharmacol 2023;70:49–55. https://doi.org/10.1016/j.euroneuro.2023.02.010.

[6] Martinotti G, et al. Real-world experience of esketamine use to manage treatment-resistant depression: a multicentric study on safety and effectiveness (REAL-ESK study). J Affect Disord Sep. 2022;319:646–54. https://doi.org/10.1016/j.jad.2022.09.043.

[7] Miron J-P, Jodoin VD, Lespérance P, Blumberger DM. Repetitive transcranial magnetic stimulation for major depressive disorder: basic principles and future directions. Ther. Adv. Psychopharmacol. 2021;11:20451253211042696. https://doi.org/10.1177/20451253211042696.

[8] Miuli A, et al. Hypomanic/manic switch after transcranial magnetic stimulation in mood disorders: a systematic review and meta-analysis. World J Psychiatr Aug. 2021;11(8):477–90. https://doi.org/10.5498/wjp.v11.i8.477.

[9] Martinotti G, et al. Treating bipolar depression with esketamine: safety and effectiveness data from a naturalistic multicentric study on esketamine in bipolar versus unipolar treatment-resistant depression. Bipolar Disord 2023;n/a(n/a). https://doi.org/10.1111/bdi.13296.

Mauro Pettorruso
Department of Neurosciences, Imaging and Clinical Sciences, Università Degli Studi G. D'Annunzio, Chieti, Italy
Department of Mental Health, ASL 2 Abruzzo Lanciano-Vasto-Chieti, Chieti, Italy

Giacomo d'Andrea*, Francesco Di Carlo
Department of Neurosciences, Imaging and Clinical Sciences, Università Degli Studi G. D'Annunzio, Chieti, Italy

Luisa De Risio
Department of Mental Health and Addiction, ASL Roma 5, Rome, Italy

Francesca Zoratto
Centre for Behavioural Sciences and Mental Health, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161, Rome, Italy
Unit of Cognitive Primatology, Institute of Cognitive Sciences and Technologies, National Research Council of Italy, Via Ulisse Aldrovandi 16/b, 00197, Rome, Italy

Andrea Miuli
Department of Mental Health, ASL 2 Abruzzo Lanciano-Vasto-Chieti, Chieti, Italy

Beatrice Benatti, Matteo Vismara
Department of Biomedical and Clinical Sciences Luigi Sacco and Aldo Ravelli Center for Neurotechnology and Brain Therapeutic, University of Milan, Milano, Italy

Enrico Pompili, Giuseppe Nicolò
Department of Mental Health and Addiction, ASL Roma 5, Rome, Italy

Cinzia Niolu, Alberto Siracusano
Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy

Stefano S. Sensi
Department of Neurosciences, Imaging and Clinical Sciences, Università Degli Studi G. D'Annunzio, Chieti, Italy

Bernardo Dell'Osso
Department of Biomedical and Clinical Sciences Luigi Sacco and Aldo Ravelli Center for Neurotechnology and Brain Therapeutic, University of Milan, Milano, Italy

Giorgio Di Lorenzo
Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy
IRCCS Fondazione Santa Lucia, Rome, Italy

Giovanni Martinotti
Department of Neurosciences, Imaging and Clinical Sciences, Università Degli Studi G. D'Annunzio, Chieti, Italy
Department of Mental Health, ASL 2 Abruzzo Lanciano-Vasto-Chieti, Chieti, Italy
Psychopharmacology, Drug Misuse and Novel Psychoactive Substances Research Unit, School of Life and Medical Sciences, University of Hertfordshire, Hatfield, AL10 9AB, UK

* Corresponding author. Department of Neurosciences, Imaging and Clinical Sciences, Università degli Studi G. D'Annunzio, Via dei Vestini, 66100, Chieti, Italy.
E-mail address: giacomo.dandrea1993@gmail.com (G. d'Andrea).