Transcranial static magnetic stimulation for amyotrophic lateral sclerosis: a bicentric, randomised, double-blind placebo-controlled phase 2 trial

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Summary

Background Enhanced glutamatergic transmission leading to motor neuron death is considered the major pathophysiological mechanism of amyotrophic lateral sclerosis (ALS). Motor cortex excitability can be suppressed by transcranial static magnetic stimulation (tSMS), thus tSMS can be evaluated as a potential treatment for ALS. The aim of present study was to investigate the efficacy and safety of tSMS in ALS.

Methods In this phase 2 trial, we randomly assigned ALS patients to receive daily tSMS or placebo stimulation over a period of 6 months. For each participant we calculated mean disease monthly progression rate (MPR) as the variation of the total ALS Functional Rating Scale-Revised (ALSRFS-R) score, before the beginning of the treatment (over a period of at least three months) and over the six-month treatment period. The primary efficacy outcome was the difference in MPR before and after the beginning of treatment. Secondary outcomes included safety and tolerability, compliance, and changes in corticospinal output. A long-term follow-up of 18 months was performed in all patients who completed the six-month treatment considering a composite endpoint event (tracheostomy or death). Trial registered at ClinicalTrials.gov, ID: NCT04393467, status: closed.

Findings Forty participants were randomly assigned to real (n = 21) or placebo stimulation (n = 19). Thirty-two participants (18 real and 14 placebo) completed the 6-month treatment. The MPR did not show statistically significant differences between the two arms during the pre-treatment (mean ± Standard deviation; Real: 1.02 ± 0.62, Sham: 1.02 ± 0.57, p-value = 1.00) and treatment period (Real: 0.90 ± 0.55, Sham: 0.94 ± 0.55, p-value = 0.83). Results for secondary clinical endpoints showed that the treatment is feasible and safe, being compliance with tSMS high. The change in corticospinal output did not differ significantly between the two groups. At the end of the long-term follow-up of 18 months, patients of real group had a statistically significant higher tracheostomy-free survival compared with patients of placebo group (Hazard Ratio = 0.27 95% Confidence interval 0.09–0.80, p-value = 0.019).

Interpretation tSMS did not modify disease progression during the 6 months of treatment. However, long-term follow-up revealed a substantial increase in tracheostomy free survival in patients treated with real stimulation supporting the evaluation of tSMS in larger and more prolonged studies.

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Research in context

Evidence before this study

Our randomized controlled trial investigates the efficacy and safety of transcranial static magnetic stimulation (tSMS) as a potential treatment for amyotrophic lateral sclerosis (ALS). To date, no treatments are available that significantly modify the course of ALS. Both glutamatergic excitatory neurotransmission and oxidative damage are associated with neurodegeneration in ALS. Among FDA-approved medications, riluzole targets glutamatergic excitatory neurotransmission, whereas edaravone and tofersen target oxidative damage. Tofersen has been approved for patients with mutations of superoxide dismutase 1 (SOD1) gene encoding for a powerful antioxidant enzyme protecting cells from superoxide radicals' toxicity. Mutant SOD1 protein is toxic for motor neurons and tofersen has been designed to reduce the synthesis of this protein.

A non-pharmacological approach to counteract excitotoxicity has been evaluated in several small trials using non-invasive neuromodulation techniques, namely transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) of the primary motor cortex or invasive epidural cortical stimulation. We retrieved all these studies of therapeutic brain stimulation in ALS from the PubMed database, published from 2004 to 2023, which we also reviewed in a recent article. Overall, these studies provide preliminary evidence on a variable effect of neuromodulation in determining a slight slowing of ALS progression. Still, treatment type, duration, and frequency might represent critical factors in obtaining clinically significant results.

Added value of this study

In a double-blind study design, followed by an open-label phase, we assessed the efficacy and safety of a newly introduced non-invasive neuromodulation approach, the tSMS, allowing a prolonged magnetic field exposure of the target brain areas to increase the treatment dosage.

In the present study, tSMS did not modify ALS progression during the six months of double-blind treatment. However, long-term follow-up revealed a substantial increase in tracheostomy-free survival in treated patients, supporting the evaluation of tSMS in larger and more prolonged studies.

Implications of all the available evidence

Present results indicate that tSMS should be considered as a non-invasive neuromodulation tool with potential therapeutic usefulness in ALS, deserving further investigation and possibly a better-tailored approach. Indeed, our study suggests a long-term effect of stimulation and confirms that the treatment is feasible, safe, and associated with high compliance. The biophysical characteristics of tSMS also allow for self-administration at the patient's home multiple times daily, making it suitable for potential routine clinical usage.

Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease without cure, leading to death on average within three years of symptom onset. Excitotoxicity mediated by an enhanced response of motor neurons to glutamatergic inputs leading to neuronal death is considered a major pathophysiological mechanism of ALS.[1] In human ALS, an abnormal response of the upper motor neurons (UMN) to excitatory inputs has been demonstrated using non-invasive transcranial magnetic stimulation (TMS) of the brain since the early phases of the disease.[2,3] Recent studies further suggest that motor cortex changes can also trigger lower motor neuron degeneration.[4] The main current pharmacological treatment is riluzole which targets glutamatergic neurotransmission in the attempt to reduce excitotoxicity even if its precise mechanism of action is not completely explained.[5] However, the disease-modifying effect of riluzole, a glutamate-release inhibitor approved by the Food and Drug Administration (FDA) and European Medical Agency (EMA) for ALS, is rather limited. Currently, only 3 medications are FDA approved for ALS treatment: riluzole, edaravone, and tofersen, an intrathecally administered antisense oligonucleotide, reducing the synthesis of the superoxide dismutase 1 (SOD1) protein for patients with ALS associated with mutations in SOD1 gene.[6]

Motor cortex excitatory neurotransmission can be modulated using repetitive TMS (rTMS).[7] The potential therapeutic effects of rTMS protocols capable of reducing motor cortex excitability have been tested in several studies as a non-pharmacological approach to antagonize excitotoxicity.[8] These studies demonstrated a slight but significant reduction of ALS progression correlated with the duration and the frequency of treatments. Based on these findings, it can be hypothesized that intensive protocols of rTMS might result in a more pronounced effect. However, there are main limitations in the therapeutic use of rTMS: its after-effects are short-lived, and it can be performed only in clinical settings, with high costs. Thus, the feasibility of intensive stimulation in ALS patients who have an increasing disability remains challenging. These limitations can be overcome by using the transcranial direct current stimulation (tDCS) that can be performed even at patient's home, being based on battery-driven

devices,[9] or by using chronic invasive brain neurostimulation through implanted electrodes. Transcranial DCS protocols capable of suppressing corticospinal excitability have been evaluated in pilot studies, but the results are controversial, with one study, based on cortico-spinal DCS, reporting a positive effect on muscle strength but not on functional outcome,[10] and the other study reporting no effect or even enhanced disease progression.[11] Epidural motor cortex stimulation (eMCS), an invasive form of brain stimulation that uses electrodes implanted over the dura, produces physiologic effects comparable to those of rTMS.[12] The potential of eMCS has been evaluated in a single patient with rapidly progressive ALS who survived for more than 15 years after implantation.[13] The benefits of eMCS in ALS were recently confirmed in a murine model of the disease.[14] The dose-dependent effects of non-invasive rTMS and the pronounced effect of eMCS in humans and animals support the hypothesis that chronic motor cortex stimulation might be effective in slowing ALS progression.

Recently, a new technique of non-invasive stimulation, termed transcranial static magnetic field stimulation (tSMS), has been introduced. It is based on exposure to a static magnetic field produced by a cylindrical neodymium magnet placed over the scalp trough a helmet.[15] When tSMS is applied to the motor cortex of healthy subjects for 10–30 min, it can suppress its excitability.[16] Even though tSMS can reduce motor cortex excitability as rTMS and tDCS inhibitory protocols, the mechanisms of action of tSMS are still poorly defined. Studies in humans with epidural spinal electrodes in whom it is possible to record directly corticospinal activity have shown that rTMS and tDCS produce a direct modulation of corticospinal output suppressing the repetitive discharge of pyramidal cells.[17] Regarding tSMS, there is converging evidence from experimental studies suggesting a modulation of ionic interchange across the membrane that is responsible for its physiological effects at the cellular/synaptic level.[15,18,19] Interestingly, a recent study in motor cortical slices of mice, showed that the decrease in neuronal excitability induced by static magnetic stimulation is produced by an enhancement in shunting inhibition via a plasma membrane chloride channel with a reduced repetitive action potential firing of pyramidal neurons.[20] Since tSMS does not require any electronic equipment, it can be easily performed multiple times daily at patients' home to obtain chronic suppression of cortical excitability. Transcranial SMS has been recently evaluated for treating dyskinesias in Parkinson's disease with evidence of significant subjective benefit.[21] In a pilot study, we recently evaluated the effects of chronic home-based tSMS treatment, performed three times a day, in two patients with rapidly progressive ALS.[22] The study showed that daily tSMS is feasible and safe; moreover, a dramatic and prolonged reduction in disease progression was observed. Considering that both patients had a rapidly progressive form of ALS, the fact that they remained quite stable for years suggests that multiple daily sessions of tSMS may significantly modify disease progression.[23]

Here, we describe the results of a phase 2, randomized, placebo-controlled trial evaluating the safety and efficacy of chronic tSMS in patients with sporadic ALS.

Methods

This was a bicentric, placebo-controlled, randomized, and double-blind phase 2 trial conducted from May 2020 through July 2022 at two Italian ALS Centers: "Campus Bio-Medico University of Rome" and "Istituto Auxologico Italiano IRCCS" of Milan. It included a pre-treatment observation period of at least three months to evaluate disease progression in individual patients before the beginning of treatment followed by a six-month intervention period. The trial was conducted in accordance with the Good Clinical Practice guidelines of the International Conference on Harmonisation and the ethical principles of the Declaration of Helsinki. Protocol approval was provided by the Ethics Committee of the two trial sites and by the section for Medical Devices of the Italian Ministry of Health. Written informed consent was provided by the participants before screening. The trial has been registered at ClinicalTrials.gov, ID: NCT04393467.

With Ethical Committee approval, after the conclusion of the six-month period of treatment, open-label real stimulation was offered both to patients who had undergone real and to patients who had undergone placebo stimulation.

Trial participants

The trial enrolled adults with a diagnosis of ALS as determined by revised El Escorial[23] and Awaji-Shima criteria[24] within 24 months after symptom onset. Additional eligibility criteria included: 1) age between 18 and 75 years; 2) total score on the ALS Functional Rating Scale–Revised (ALSFRS-R)[25] >30 at the recruitment; 3) a decrease in the pre-randomization observation period of the ALSFRS-R score of at least 0.3 points per month; 4) normal respiratory function with a forced vital capacity >80% and a total score >4 at the recruitment on ALSFRS-R items evaluating respiratory function (items 10, 11, 12); 5) treatment with riluzole 50 mg twice a day. The choice to include patients on riluzole was done in accordance with FDA recommendation of add-on designs, in which a treatment previously shown to be effective for the treatment of ALS is given to all patients participating in the trial. Exclusion criteria were: 1) participation in other clinical trials; 2) tracheostomy and/or percutaneous gastrostomy (PEG); 3) contraindications to magnetic field exposure; 4) pregnancy or

breast-feeding; 5) history of epilepsy or seizures; 6) current treatment with drugs acting on central nervous system except for antidepressant drugs and benzodiazepines; 7) cognitive impairment. Patients were recruited mainly from the ALS population followed at the two participating centers but also patients referred from other centers were considered.

Study design

At recruitment, patients were clinically evaluated calculating the ALSFRS-R score (T0: Recruitment). After a pre-treatment observation period of at least three months, patients were randomly assigned to either real tSMS or placebo (sham) tSMS group (T1: Randomization). At this time, a new clinical evaluation with ALSFRS-R administration and TMS assessment of the corticospinal excitability were performed. TSMS treatment was then started and performed for 6 months. At the end of this double-blind treatment period (T2), patients of both arms underwent a new clinical and TMS assessment. Afterwards, open-label real stimulation was offered to all recruited patients: tracheostomy-free survival was monitored during this study extension period. The flowchart of the study is reported in Fig. 1.

There were neither deviations from the protocol nor protocol amendments affecting trial recruitment or conduct during the study.

Randomization

Randomization was based on a simple randomization method using a pre-determined allocation list with a 1:1 ratio, extracted by software and managed by a co-author who was not involved in patients' evaluations. Subjects were sequentially allocated to either treatment or control group following the list order. The tSMS device was delivered to the patients for home self-administration by a co-author not involved in patients' evaluations.

Trial interventions and procedures

Outcomes

In each patient, we calculated the mean disease monthly progression rate (MPR) as the variation of the total ALSFRS-R score measured at T0 and T1 divided by the months of observation (before the beginning of the treatment) and the variation between T1 and T2 divided by six-months (over the treatment period). The primary efficacy outcome was the difference in MPR before (from T0 to T1) and during the six-month treatment (from T1 to T2).

Secondary outcomes were: 1) safety and tolerability evaluated as incidence of adverse events during the stimulation period; 2) compliance evaluated as the number of stimulation sessions actually completed by each patient assessed by means of patients' reports collected monthly or daily with phone calls or at the time of clinical evaluations or via electronic devices; patients were also asked to specify in the report the duration of each stimulation session; 3) effects of tSMS on corticospinal output evaluated as percentage change in motor evoked potential (MEP) amplitude between T1 and T2.

We did not use a structured questionnaire to evaluate placebo effect or stimulation related pain/discomfort;

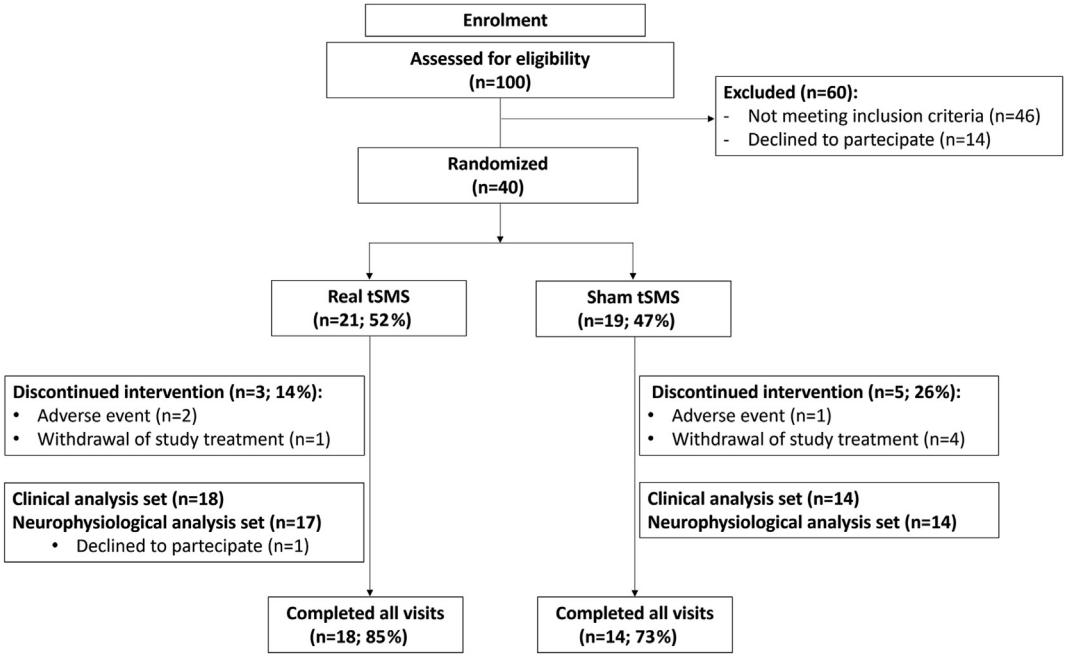

Fig. 1: Flowchart of the study: participants' enrolment, randomization, and analysis.

however, patients were instructed at the beginning of the study to report any side/adverse event and specifically asked for any side/adverse effect on occasion of clinical evaluations or phone calls monitoring of treatment adherence.

Post-hoc analysis: long-term follow-up. We evaluated the disease progression (survival analysis) during an extended follow-up of 18 months starting from T2. In this long-term follow-up were included only patients who had completed the original 6-month treatment period (from T1 to T2). The patients were grouped according to their initial trial-group randomization regardless of switching from sham to real treatment at the end of the study. A composite endpoint event (tracheostomy or death) was considered in this post-hoc analysis comparing the long-term follow-up in patients in the real stimulation arm with that observed in patients treated with sham stimulation or sham stimulation followed by delayed real stimulation started after the six-month follow-up visit.

Procedures

Transcranial static magnetic field stimulation

To deliver tSMS we used a cylindrical Nickel-plated NdFeB magnet of 60 mm diameter, 30 mm of thickness and a weight of 0.67 Kg, with a nominal field strength of ~120 Kg (MAG60r/MAG60s, Neurek SL, Toledo, Spain), held in place by an ergonomic helmet specifically designed to target the motor cortex (MAGmv1.1, Neurek). An additional non-magnetic steel nickel-coated cylinder (MAG60s, Neurek) was located in the helmet over the contralateral motor cortex to counterbalance the weight of the active magnet. The MAG60s has the same size and weight of the MAG60r. The total weight of the stimulation system is ~2 Kg. We trained patients and caregivers to the use of the helmet at the beginning of the study and the first trial of tSMS was performed at the hospital under direct supervision. For chronic treatment, tSMS was self-administered at patients' home, for 3 times every day at least 4 h apart; in each session tSMS was applied sequentially for 20 min over each motor cortex. To prevent displacement of the helmet patients were instructed to rest during stimulation.

Evaluation of corticospinal output using transcranial magnetic stimulation

We evaluated the effect of chronic tSMS on corticospinal output to hand muscles using TMS. We recorded MEPs before the beginning of tSMS and at the end of the six-month period of stimulation. MEPs were recorded from abductor pollicis brevis muscle (for patients studied in Milan) or from the abductor digiti minimi muscle (for patients studied in Rome). TMS was performed using a Magstim 200[2] stimulator (The Magstim Co. Ltd., Whitland, UK) at an intensity of 100% of maximal stimulator output.

Statistical analysis

The normality of continuous variables has been evaluated by means of graphical inspection (QQ plot) and Shapiro–Wilk test. Continuous variables are shown as mean and standard deviation (or median and interquartile range in case of non-normal data), while categorical variables are shown as absolute and relative frequencies. Unpaired T-test (or Wilcoxon rank-sum test in case of non-normal data) was used to compare the continuous variables between groups and Chi-square (or Fisher's exact test) for categorical ones. Moreover, for T-test, when the group variances were not homogeneous (based on F-test), the Satterthwaite correction of effective degrees of freedom was applied.

For the primary outcome (MPR), a repeated measurements ANOVA model was implemented by a linear mixed model considering the observation at different time as repeated measurements within patients. The correlation between measurements was modelled through the compound symmetry matrix. The model included the following covariates: time (T0 to T1 and T1 to T2), group (Real and Sham), and their interaction. Only patients who completed the 6-month treatment were included in the analysis. For post-hoc analysis, Kaplan–Meier curves and associated log-rank test were applied to test differences between groups. We included all the patients who completed the 6-month treatment period who were also included in the primary outcome analysis. We performed a proportional hazards Cox model to estimate Hazard Ratio and its 95% confidence interval (95% CI) of composite endpoint event (tracheostomy or death) associated with Real or Sham group. The assumption of proportional hazards was verified by means of the method of inclusion of time dependent covariate.

For both analyses, in presence of significant findings we further performed sensitivity analyses. The first, aimed to take into account the potential unbalanced distribution of patient characteristics, was carried out using weighted regression model in which each patient was weighted by the inverse probability-of-treatment received (IPTW approach) To estimate the weight, a logistic regression model was fitted considering the group as dependent and age, gender, ALS phenotype at disease onset and mean ALSFRS-R score at T0 as covariates.[26] The second one, aimed to verify the impact of selection bias due to missing outcome data, was performed applying the IPW approach, based on the same rationale of IPTW approach, with weights obtained by a logistic regression model with non-missingness status as dependent variable and the same covariates used in IPTW approach plus group.[27]

For all hypothesis tests, a p-value less than 0.05 was considered statistically significant. All statistical analysis was performed using SAS software (SAS, Version 9.4; SAS Institute, Cary, North Carolina, USA).

We planned to enroll 40 participants randomized 1:1 to real stimulation or sham stimulation. This sample size achieves 80% power to reject the null hypothesis of equal means when the population MPR mean difference is 0.45 assuming a standard deviation for both groups of 0.5 and an alpha of 0.05 using a two-sided two-sample equal-variance t-test.[28] We also tried to reduce the effect of the pronounced interindividual variability in ALS progression including only patients with a clear evidence of disease progression as demonstrated by a decrease of the ALSFRS-R score of at least 0.3 points per month in the pre-randomization observation period. Due to the limited sample size, no analyses on gender effect on outcomes could be performed.

Role of the funding source

The study was investigator-initiated with Campus Bio-Medico University as sponsor. Funding was provided by "Fondazione 'Nicola Irti' per le opere di carità e di cultura". "Fondazione 'Nicola Irti' per le opere di carità e di cultura" had no role in final study design, data collection, analysis and interpretation, manuscript preparation, or the decision to submit for publication.

Results

One-hundred patients were screened for the study (Fig. 1). Forty-six patients did not meet inclusion/exclusion criteria and 14 patients declined to participate. Forty participants were randomly assigned either to real (n = 21) or to placebo stimulation (n = 19). The patients had no relevant co-morbidity, in particular they had no other neurological disorder.

The patients had no family history of ALS, and genetic testing for the main ALS genes (*C9ORF72, SOD1, TARDBP,* and *FUS*) was negative. The demographic and clinical characteristics of the real and sham patients are reported in Table 1: there were no statistically or clinically significant differences between groups at baseline. Four participants in the placebo group and one in the real group decided to discontinue the stimulation before the conclusion of the study. Thus, they did not complete the six-month stimulation period. Moreover, one patient in the placebo group and two in the real group died or underwent tracheostomy within six months after randomization.

Primary outcome: effects on disease progression

The primary outcome analysis was conducted on the 32 subjects who completed the six-month treatment period (real group: n = 18; sham group: n = 14). Fig. 2 shows, in Panel A, the median values and interquartile ranges of ALSFRS-R at different time points by treatment arm, and, in Panel B, the same statistics for MPR.

All patients showed a decline over time. In particular, considering "pre-randomization" and "six months after randomization" measurements (mean ± SD), similar group-specific decrements were observed (from 40.3 to 31.0 and from 37.7 to 28.2 for patients of real and sham groups, respectively). The MPR did not show statistically significant differences between the two arms during the pre-treatment observation, i.e., from T0 to T1 (Real: 1.02 ± 0.62, Sham: 1.02 ± 0.57, p-value = 1.00) and during the treatment period, i.e., from T1 to T2, (Real: 0.90 ± 0.55, Sham: 0.94 ± 0.55, p-value = 0.83). Analogously, the change of MPR during time was not statistically different between groups (p-value = 0.86).

Long-term follow-up

Long-term follow-up after the end of the six-month double-blind study was performed in the 32 patients who completed it.

Ten out of 18 patients in the real group decided to continue stimulation and 6 out of 14 patients in the placebo group decided to switch to real stimulation.

	All participants (n = 40)	Real tSMS (n = 21)	Sham tSMS (n = 19)
Sex			
Male	25 (62%)	12 (57%)	13 (68%)
Female	15 (37%)	9 (43%)	6 (31%)
Age (years), mean (SD)	57.5 (11)	55.3 (12)	60.2 (9)
ALS phenotype at disease onset			
Bulbar	7 (17%)	3 (14%)	4 (21%)
Spinal	33 (83%)	18 (86%)	15 (79%)
Disease duration (months), mean (SD)	24.1 (7.9)	24.5 (7.1)	23.7 (8.6)
ALSFRS-R score at T0, median [IQR]	39 [37–42]	40 [39–42]	38 [34–43]
ALSFRS-R score at T1, median [IQR]	36 [31–38]	37 [33–39]	35 [27–37]
MPR pre-randomization, median [IQR]	1.00 [0.67–1.48]	1.00 [0.67–1.20]	1.17 [0.67–1.67]

ALS: amyotrophic lateral sclerosis; ALSFRS-R: Revised ALS Functional Rating Scale; tSMS: transcranial Static Magnetic Stimulation. IQR: interquartile range; SD: standard deviation; T0: time of recruitment; T1: time of randomization; MPR: monthly progression rate (see Methods). Data are presented as n (%) or mean (SD) or median [IQR]. Percentages are based on the number of participants in each treatment group for the population being analyzed. Disease duration is measured at the time of randomization (T1).

Table 1: **Demographics and clinical characteristics by treatment group.**

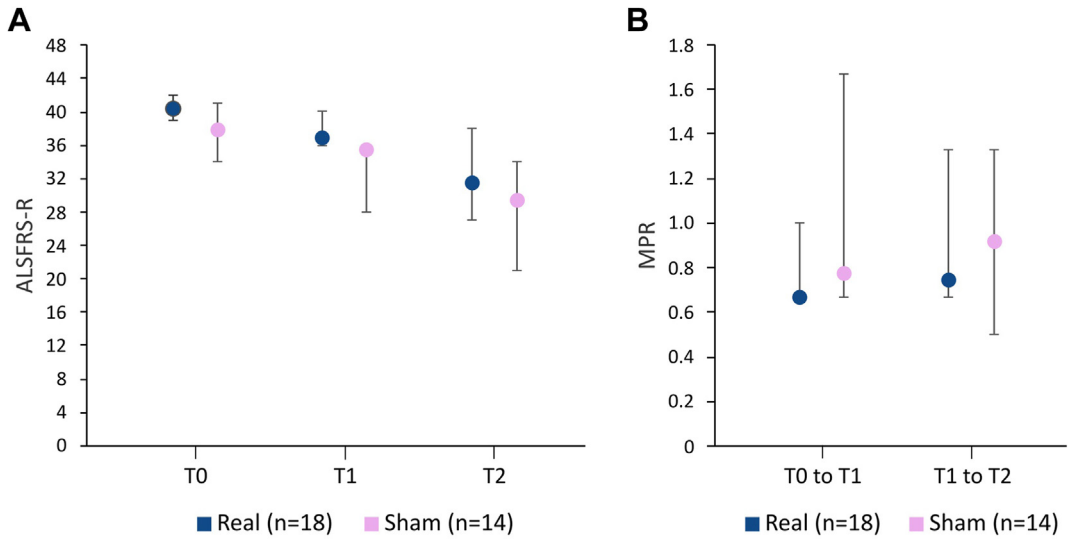

Fig. 2: ALSFRS-R (panel A) and monthly progression rate (MPR) (panel B) median values and interquartile ranges at different time points by treatment arm. MPR is calculated as the ALSFRS-R variation divided by the months of observation, for each period of interest. T0: recruitment; T1: randomization; T2: end of 6-month blind tSMS treatment.

The last patient completed the long-term follow-up in January 2024. Two patients (1 real and 1 placebo) were no longer contactable and thus, they were lost to the follow-up. The median follow-up time was 18 months (IQR 10–18 months). As shown in Fig. 3, at the end of the long-term follow-up 13 patients in the real group and 4 patients in the sham group were alive and tracheostomy free with a statistically significant higher tracheostomy-free survival in the real group compared with the sham/delayed real stimulation group (p-value = 0.011). The association between group (Real vs Sham) and tracheostomy/death was HR = 0.27 (95% CI 0.09 to 0.80,

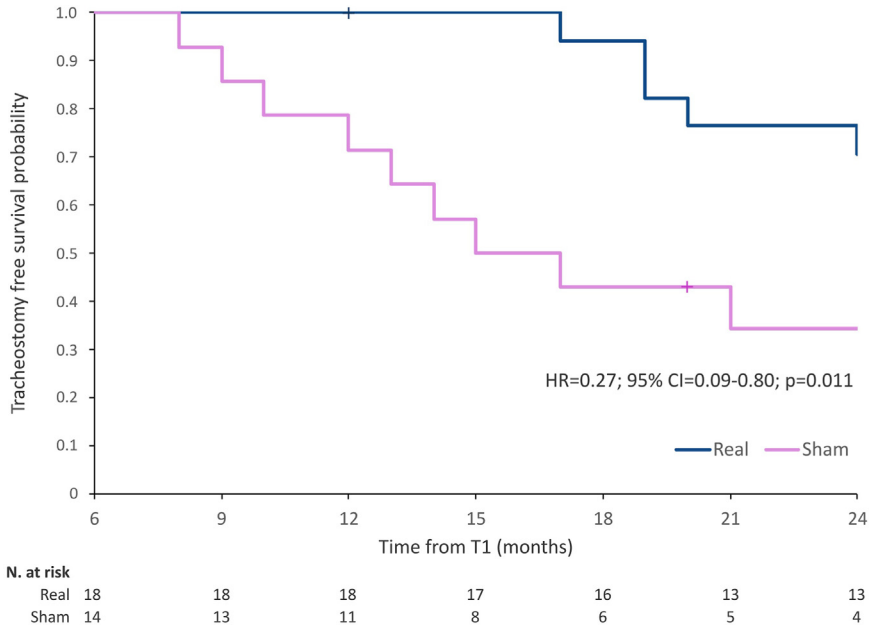

Fig. 3: Tracheostomy-free survival according to the treatment group, as evaluated during the extended follow-up phase of the study (i.e., starting at the completion of the 6-month double-blind treatment period). Real group: dark blue line; Sham group: purple line. +: censored patients. HR: hazard ratio; CI: confidence interval.

p-value = 0.019) and it remained statistically significant after adjustments for age, MPR at baseline and ALS phenotype at disease onset (HR = 0.30).

The sensitivity analyses showed similar results (IPTW approach: HR = 0.45, 95% CI 0.20 to 0.98, p-value = 0.044 and IPW approach: HR = 0.25, 95% CI 0.09 to 0.68, p-value = 0.007). Moreover, 2 out of 4 patients in the sham group had undergone PEG positioning while all patients in the real group were PEG-free.

Secondary outcomes

Safety and tolerability

The retention rate at T2 was 80%. Overall, 11 patients (27.5%) reported treatment-emergent adverse events (TEAEs), of which 6 (28.6%) in the real group and 5 (26.3%) in the sham group. Of these events, only 4 (10%) could have a probable, possible, or definite relationship to the intervention, so they were defined as treatment-related AEs. They were mild and included headache (n = 2 in the real group), which was transitory in the first weeks of treatment, and cervical pain (n = 1 in the real group and n = 1 in the sham group), attributed to the device weight (most patients needed a headrest to sustain the helmet during the procedure). In the real group, cervical pain was the cause of treatment and study withdrawal in one patient. Serious AEs were 7 (17.5%) in the overall population (n = 4 in the real group and n = 3 in the sham), but no one was related to treatment. Serious AEs included pulmonary embolism, respiratory failure, and worsening of dysphagia requiring tracheostomy and PEG positioning. As reported above, one patient in the real group and one in the sham group died within six months after randomization as a consequence of ALS progression (one patient in the sham group presented a worsening of dysphagia but refused PEG positioning). A summary of the distribution of TEAEs and a list of the major AEs are reported in Table 2 and Table 3.

Compliance

Compliance was assessed by means of a diary that patients (or caregivers) were instructed to keep, and it was reported as a percentage of completed tSMS sessions. Compliance was high in both groups, with a medium value of 92%.

Effects of tSMS on corticospinal output

We analyzed the effects of tSMS on corticospinal output to hand muscles evaluated as MEP amplitude change between T1 and T2. Data were available for 16 patients in the real group and 10 patients in the sham group, all these patients were included in the final analysis.

A decrease in MEP amplitude at T2 was observed in both groups (Real: –31.0%; Sham: –48.0%). However, the comparison of changes between randomization groups was not significant (p-value = 0.62).

Discussion

Cortical hyperexcitability characterizes ALS since the early phases and even in the pre-symptomatic stage of the disease and it is believed to underlie corticospinal cell degeneration.[3] In the present study, we used prolonged non-invasive stimulation suppressing motor cortex excitability with the aim to mitigate excitoxicity and to reduce ALS progression. To this end, we selected tSMS, a neuromodulation technique capable of reducing motor cortex excitability suitable for home-based treatments and thus ideal for intensive and

	All participants (n = 40)	Real-tSMS (n = 21)	Sham-tSMS (n = 19)
TEAEs	11 (28%)	6 (29%)	5 (26%)
Treatment-related TEAEs	4 (10%)	3 (14%)	1 (5%)
Treatment-related serious TEAEs	0 (0%)	0 (0%)	0 (0%)
Participants with TEAEs by maximum severity			
Mild	4 (10%)	3 (14%)	1 (5%)
Moderate	1 (5%)	1 (5%)	0 (0%)
Severe	7 (18%)	4 (19%)	3 (16%)
Potentially life-threatening	0 (0%)	0 (0%)	0 (0%)
SAEs	7 (18%)	4 (19%)	3 (16%)
Participants with treatment-related SAEs	0 (0%)	0 (0%)	0 (0%)
Participants with TEAEs resulting in treatment withdrawal	2 (5%)	2 (10%)	0 (0%)
Participants with TEAEs resulting in withdrawal from study	2 (5%)	2 (10%)	0 (0%)
Participants with TEAEs resulting in death	2 (5%)	1 (5%)	1 (5%)

TEAE: treatment-emergent adverse event; tSMS: transcranial Static Magnetic Stimulation; SAEs: serious adverse events. Values are reported as n (%) and divided by treatment group. Percentages are based on the number of participants in a given treatment group divided by the population being analyzed. A TEAE is defined as any adverse event started after the initiation of tSMS. Treatment-related AEs are TEAEs that are considered to have a probable, possible, or definite relationship to the intervention.

Table 2: **Overall summary of adverse events by treatment group: population safety.**

	Real-tSMS (n = 21)	Sham-tSMS (n = 19)
Headache	2 (10%)	0 (0%)
Cervical pain	1 (5%)	1 (5%)
Pulmonary embolism	0 (0%)	2 (11%)
Deep venous thrombosis	1 (5%)	0 (0%)
Respiratory failure leading to NIV	1 (5%)	0 (0%)
Respiratory failure leading to tracheostomy	1 (5%)	1 (5%)
Worsening of dysphagia (PEG refusal)	0 (0%)	1 (5%)
Worsening of dysphagia leading to PEG positioning	1 (5%)	0 (0%)
Death	1 (5%)	1 (5%)

tSMS: transcranial Static Magnetic Stimulation; NIV: non-invasive ventilation; PEG: percutaneous endoscopic gastrostomy. Data are reported as n (%). Percentages are based on the number of participants in a given treatment group divided by the population being analyzed.

Table 3: **Participants with adverse events by treatment group.**

prolonged protocols of daily stimulation. Because the rate of disease progression is variable in ALS,[29,30] we considered as primary outcome the change in monthly rate of disease progression. The definition of likely course in individual patients and the inclusion of patients with clear evidence of disease progression can minimize the confounding effects of disease progression variability[31] and enhance the possibility of attaining adequate statistical power with a limited sample size. Moreover, we evaluated the change in the amplitude of MEPs recorded in hand muscles after motor cortex stimulation as a secondary outcome. MEPs represent an indirect measure of corticospinal projection function[32] and, thus, they can be considered a neurophysiological biomarker of corticospinal tract degeneration.

In this double-blind, randomized, placebo-controlled, phase 2 trial evaluating tSMS effects in patients with sporadic ALS, there was no difference between treatment groups in the primary endpoint of change of MPR during the first six months of treatment. However, the long-term follow-up extended to 18 months after the end of the study, revealed a substantial increase in tracheostomy-free survival in patients treated with real stimulation when compared with patients who underwent sham stimulation during the first six months of treatment. The tracheostomy-free survival was almost doubled in the real group at the end of the follow-up, and the HR was 0.27.

Although the difference between real and sham stimulation groups is very pronounced, the clinical implication of this finding should consider the low precision of effect estimates, represented in a wide 95% CI (i.e., 0.20 to 0.98 for the HR). Moreover, this result needs to be interpreted with caution because the long-term follow-up represents a post-hoc analysis. On the other side, the most recent clinical trials on ALS tend to indicate that the efficacy of any treatment needs to be evaluated after a prolonged period of observation. The results of trials with sodium phenylbutyrate-taurursodiol[33] and with tofersen for SOD1 ALS[6] strongly support the need of long-term observation to detect the efficacy of treatments on clinical parameters and pertinent biomarkers. Many works underline the heterogeneity of ALS patients making it difficult to determine if a disease-modifying therapy is effectively slowing progression.[34] The need for a prolonged period of treatment to attain clinical effects is also suggested by our single case study evaluating the effects of epidural motor cortex stimulation in ALS. In this patient, no effect was observed during the first 22 months of stimulation, but a very pronounced reduction in MPR was observed in the following period.[13]

The effect of riluzole, even in the most severe stages of the disease, further supports the idea that glutamate-related excitotoxicity can be a therapeutic target throughout the entire course of the disease.[35]

The analysis of the secondary outcomes shows that the treatment is feasible and well tolerated as demonstrated by the high retention rate at the end of the six months of treatment (80%) and the high adherence to the treatment (92% of compliance). Moreover, the treatment is safe as demonstrated by the low number of patients (10%) who experienced treatment-related adverse events that, in any case, were mild and reversible.

Previous studies have shown that tSMS is safe in healthy humans in that tSMS application for 2 h did not induce neural or glial damage as assessed by serum levels of neuron-specific enolase and S-100 protein.[36] Moreover, in a clinical trial in patients with advanced Parkinson's disease, the application of tSMS over the motor cortex (10 sessions over two weeks) did not produce any relevant adverse event.[21] Present findings extend the safety of repeated sessions of tSMS in patients with neurodegenerative diseases. It should also be considered that the magnetic flux density at cortical level during tSMS exposure is below 200 mT,[37–39] a value which is one order of magnitude below the International Commission on Non-Ionizing Radiation Protection limit for occupational exposure.[40] Thus, it is highly unlikely that tSMS may induce local damage.

The neurophysiological assessment reveals an overall reduction of MEP amplitude over the six-month treatment period, without a significant difference between the study groups, which we interpret as indicative of motoneuron loss related to disease progression. However, it should be considered that we obtained these measurements only in a part of the study sample (n = 26) and that the MEP amplitude parameter, depending on both upper and lower motoneuron preservation, might not be sensitive enough to detect any cortical protective effect of neuromodulation. To this end, measuring the amplitude ratio between MEP and compound motor action potential evoked by peripheral nerve stimulation could provide a more accurate information on UMN dysfunction, although we did not have evidence of a different disease progression between treatment groups.

The helmet we used for stimulation mainly targets the lateral motor cortex corresponding to the upper limbs however, because of the relatively large magnet employed (6-cm diameter) and because of the existence of cortico-cortical connections, functional changes are conceivably induced beyond the upper limb representation in the nearby areas connected to bulbar and trunk muscles. This is supported by previous studies reporting tSMS induced excitability changes beyond the local circuits.[41–44] Interestingly, a recent study in monkey revealed that the diaphragm has two separate representations in the motor cortex one of which is located close to hand motor cortex.[45] The lateral representation of the diaphragm, that overlaps the origin of cortical projections to laryngeal muscles, might have been directly modulated by the magnet reducing excitoxicity-related neurodegeneration with positive effects on respiratory function. However, further studies targeting more directly cortical representation of respiratory and swallowing muscles might be extremely interesting.

A recent study in normal subjects demonstrated that tSMS not only suppresses the excitability of the stimulated motor cortex, but also results in a facilitation of the contralateral motor cortex possibly due to a reduction of the interhemispheric inhibition.[46] The possibility to manipulate motor cortex excitability producing opposite effects on the stimulated side and on the contralateral side has a therapeutic potential in those disorders characterized by an imbalance in motor cortex excitability such as stroke,[47] and a preliminary study by Shimomura et al.[48] suggests that tSMS of the contralesional motor cortex might have positive effects in subacute stroke. Although the contralateral effect of tSMS is short lasting,[46] it might reduce the benefit of tSMS in ALS patients due the possible enhancement of the excitability of the non-stimulated motor cortex. Thus, a concomitant bilateral motor cortex stimulation might be a better option than sequential bilateral motor cortex stimulation in ALS. We are currently exploring this approach in an ongoing proof of principle study evaluating the effects of concomitant bilateral motor cortex tSMS in ALS.

Only 10 out of 18 patients in the real group and 6 out of 14 patients in the placebo group decided to continue/start real stimulation at the end of the study. We did not investigate systematically the reasons for declining long-term stimulation thus, we can only speculate about possible reasons for this choice. All patients showed a decline over the main study and this could represent the main reason for choosing of not continuing/starting real stimulation. Another possible reason is represented by the progression of the motor deficit in particular in neck muscles that increased the discomfort associated with the wearing of the 2 Kg helmet in patients in a more advanced stage of the disease. To this end, a lighter helmet could increase the tolerability of the stimulation.

This study has several limitations. Several measures of cortical excitability such as intracortical inhibition and facilitation as evaluated by paired pulse TMS can provide additional insights on the function of corticospinal neurons and of cortico-cortical excitatory and inhibitory interneurons and might be very useful to characterize motor cortex involvement and for monitoring the progression of ALS.[49] Unfortunately, these parameters were not evaluated in present study but they represent an extremely interesting biomarker in ALS to be included in future studies.

Sample size calculation did not consider attrition, and this impacts the power of the analysis since the retention rate at the end of the 6-month blind treatment was 80%. Also, selection bias and confounding could have affected our estimates. Despite we applied IPW and IPTW approaches to try to control these errors, we cannot exclude residual confounding and systematic error due to missing outcome data in our findings.

Conclusions

In conclusion, our study demonstrates that long-term, home-based, self-administered tSMS in ALS is safe and feasible. Although the primary endpoint was not met in the study, results of the long-term follow-up strongly suggest a possible clinical efficacy of tSMS with increased tracheostomy-free survival, supporting the necessity to assess the efficacy of this innovative technique in further studies with more prolonged follow-up and a larger sample.

Contributors

VD, FR and VS conceptualized and designed the study. DS and AZ designed the statistical plan and analysis. FR, AD, MB, LM, EC, NT, GM, and FC led the investigation and collected data. All authors evaluated and interpreted the outputs from the formal data analysis. VD wrote the first draft with support from VS and FR. All authors were involved in critical review and revision of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Data sharing statement

Data collected for the study, including de-identified individual participant data and a data dictionary defining each field in the set, will be made available to others upon request.

Declaration of interests

V.S. received compensation for consulting services and/or speaking activities from AveXis, Cytokinetics, Italfarmaco, Liquidweb S.r.l., Novartis Pharma AG, and Zambon Biotech SA, and receives or has received research support from the Italian Ministry of Health, AriSLA, and E-Rare Joint Transnational Call. He is member of the Editorial Boards of *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, *European Neurology*, *American Journal of Neurodegenerative Diseases*, *Frontiers in Neurology*, and *Exploration of Neuroprotective Therapy*.

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All other authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2024.101019.

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