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RESEARCH ARTICLE

High-frequency motor rehabilitation in amyotrophic lateral sclerosis: a randomized clinical trial

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Abstract

Objective: Exercise may be physically and psychologically important for people with ALS, especially in the earlier stages of the disease, and, as a consequence, current ALS clinical management includes individualized rehabilitation as part of multidisciplinary care because. However, while recent studies focused on which type of exercise is more indicated to ALS patients, there is no evidence at which frequency training sessions should be performed. **Methods**: We performed an assessor blinded randomized clinical trial to investigate the superiority of two different frequencies of exercise on rate of progression in ALS. We enrolled 65 patients in two groups: intensive exercise regimen (IER, five sessions/week) versus usual exercise regimen (UER, two sessions/week). The primary aim was to assess if IER decreased disease progression, measured through Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised, with respect to UER. Secondary aims included assessment of adverse events, tracheostomy-free survival, motor and respiratory functions, fatigue, quality of life and caregiver burden. Treatment regimen consisted for both groups of the same kind of exercise including aerobic training, endurance training, stretching or assisted active mobilization, differing for frequency of intervention. **Results**: No significant changes in disease progression were found in patients under IER versus UER. At the end of the study, there were no significant differences between the two groups in survival, respiratory function, time to supporting procedures, and quality of life. Adverse events, fatigue, and caregiver burden were not different between the two treatment regimens. **Conclusions**: Despite some limitations, our trial demonstrated that high-frequency physical exercise was not superior to UER on ALSFRS-R scores, motor and respiratory functions, survival, fatigue, and quality of life of ALS patients.

Introduction

Amyotrophic lateral sclerosis (ALS) is a relentless progressive neurodegenerative disease with severe prognosis due to the mounting muscle atrophy and weakness later impending on muscles of respiration and swallowing; on average, death occurs within 3 years from diagnosis.[1] Despite intensive research, to date, the only FDA-approved drugs for ALS are Riluzole, which proved effective in increasing survival by 3–6 months[2] and Edaravone,

the newly approved and controversial antioxidant with demonstrated slowing of progression in a subgroup of patients.[3]

Nonetheless, the several advancements made in the field of clinical patients' management, multidisciplinary approach, and decision-making processes result in life prolongation for ALS patients.[4]

During the disease course, as a consequence of the spread and progression of muscle atrophy, cardiorespiratory deconditioning and disuse weakness ensue, which further precipitate the decreased possible motor activities, leading to inactivity. The resulting decreased strength of ligaments and tendons, joint tightness, osteoporosis, and further muscle atrophy often lead to obliged postures and subsequent pain and contractures, as well as psychological drawbacks on the patient and their caregivers.[5]

To prevent this loop of deconditioning and improve well-being, physical exercise is offered by physiatrists and physical therapists in the setting of integrated multidisciplinary care. In healthy people, exercise allows for myofibers remodeling, antioxidant and anti-inflammatory adaptation, neural plasticity, and overall positive cardiovascular, respiratory, musculoskeletal, metabolic and neuro-endocrine effects, not to mention a reinforcement effect on psychological well-being.[6] Exercise may be physically and psychologically important for people with ALS too, especially in the earlier stages of the disease and before significant muscular atrophy or deconditioning occurs.[5]

However, there is no clear evidence on which type of exercise, under which regimen and which outcome variables have to be routinely assessed in order to bring forward a safe and consistent motor rehabilitation, avoiding muscle overuse in a disease where muscles are already denervated and weakened.[5,6]

There are few randomized controlled studies on the effect of motor rehabilitation on ALS patients with lack of robust and consistent results.[5,7,8] Moreover, while those previous studies have focused on which type of exercise modality is more suitable for ALS rehabilitation, the optimal frequency of intervention to be recommended for these patients has never been investigated.

On the other hand, in other clinical conditions high-frequency exercise showed to be effective in maintaining muscle function and improving physical function, psychological distress and quality of life (QOL).[9,10]

Since we could not exclude the exercise modality (whether stretching, aerobic or resistance) or the weekly frequency at which a motor program is established may have mixed effects on ALS disease outcomes and patients safety, we carried out this multicentre, single-blind, randomized, controlled study testing the impact of an intensive physical therapy regimen, represented by higher-frequency sessions but equal range of exercise compared to the "standard" motor rehabilitation regimen offered to ALS patients.

Methods

Study design and participants

We measured the effects of motor rehabilitation under intensive exercise regimen (IER) compared to the usual exercise regimen (UER) in ALS patients in a single-blinded, randomized controlled study (RCT).

Three Italian ALS multidisciplinary centers (ALS Centre in Modena, Reggio Emilia, and Ferrara) participated in this study providing a 10 weeks long motor-rehabilitation program according to the allocation group, with long follow-up period for a total trial duration of 24 months.

Patients with a definite, probable or possible diagnosis of ALS according to El Escorial criteria with a clinical diagnosis within 18 months and aged between 18 and 86 years were considered eligible unless cognitive decline, respiratory deficit (measured by forced vital capacity (FVC) which had to be > 50%), or other (neurological or cardiorespiratory) conditions were present. Exclusion criteria were as follows: participation in other clinical trials within in the 3 months before screening, non-invasive (NIV) or invasive ventilation (IV), other neurodegenerative diseases, severe or instable medical conditions contraindicating rehabilitation treatment, pregnancy or breeding, residency outside Emilia Romagna Region, absence of multidisciplinary follow up.

Trial registration

The trial was identified on ClinicalTrials.gov with NCT02306109. After approval from Ethics Committees of Modena, Reggio Emilia and Ferrara, patients were enrolled once provided signed written consent in accordance to the declaration of Helsinki.

Intervention

Eligible patients were randomized with 1:1 allocation to IER or to UER. Each exercise program had to be composed of a mixture of aerobic, endurance, and low-load resistive training associated with stretching of retracted muscles as explicated in Table 1.

Standard operating procedures on motor rehabilitation were created and shared among physiatrists. The training was 45 min long independently of the IER or UER group; patients randomized to IER had to undergo five trainings per week, for 10 weeks of treatment period (50 trainings in total), whereas patients in UER continued with two trainings per week. After the treatment period, patients

Table 1. Motor program protocols in the two treatment arms.

		IER (n = 32)	UER (n = 33)
Frequency		5/week	2/week
Duration		45 min	45 min
Total session count		50	20
Initial evaluation		MRC strength, A.R.o.M. and P.R.o.M. at elbow, shoulder, hip, knee, and ankle. Hypertonia evaluation by Ashworth at ankle, knee, elbow. 6MWDT.	MRC strength, A.R.o.M. and P.R.o.M. at elbow, shoulder, hip, knee, and ankle. Hypertonia evaluation by Ashworth at ankle, knee, elbow. 6MWDT.
Motor programs	Aerobic training	* patients able to walk: on treadmill or cyclette; speed parameters are adjusted on moderate effort (Borg scale 3); 10 min exercise followed by 5 min break for a total of 30 min. * patients unable to walk but with residual strength: the same on cyclette.	* patients able to walk: on treadmill or cyclette; speed parameters are adjusted on moderate effort (Borg scale 3); 10 min exercise followed by 5 min break for a total of 30 min. * patients unable to walk but with residual strength: the same on cyclette.
	Endurance training	On non-affected muscles. Resistive force is the 40% of MCV, in 12–15 repeats per 2 sets for each movement. Tools or elastic ropes might be used. 5 min break between sets are required. To be done at least at 3 or more sessions.	On non-affected muscles. Resistive force is the 40% of MCV, in 12–15 repeats per 2 sets for each movement. Tools or elastic ropes might be used. 5 min break between sets are required. To be done at each session.
	Stretching or assisted active mobilization	Programs can be of short, middle or long duration; to be applied at each training session	Programs can be of short, middle or long duration for both sessions

IER, intensive exercise regimen; UER, usual exercise regimen; MRC, Medical Research Council Muscle Scale; ARoM, Active Range of Motion; PRoM, Passive Range of Motion; MCV, Muscle Contraction Velocity; 6MWDT, 6-minute walk distance test.

and trained caregivers maintained their exercise program (IER or UER) by their own with regular supervision of a physiotherapist once a month until month 12. Clinical follow up was then carried out until month 24 (Fig. 1).

Primary and secondary outcomes

The primary outcome was represented by the change in disease progression as measured by ALSFRS-R from baseline to month 12 in patients treated with IER compared to UER.

Secondary outcomes of the study were represented by comparison between IER and UER arms of the following: I) disease progression as measured by changes in ALSFRS-R scale every 3 months; II) survival; III) time to gastrostomy, NIV or IV; IV) respiratory function as measured by FVC% every 3 months; V) quality of life (assessed by ALSAQ-40 and McGill Quality of Life Questionnaire), every 6 months; VI) fatigue (assessed by fatigue severity scale (FSS)) every 6 months; VII) depression (Beck inventory scale), every 6 months; VIII) burden on caregiver (assessed by caregiver burden scale) every 6 months.

Assessments

Regular assessments were done by the neurologist and physiatrist in parallel during the treatment and follow-up period. The neurologist performed basal evaluations of the patients, which included ALSFRS-R, MRC, spirometry, evaluation of quality of life, fatigue and depression as aforementioned before treatment phase. The neurologist was blinded to the allocation group and visited the patient every 3 months until the 24th month, performing ALSFRS-R, MRC, and spirometry. ALSAQ-40, FSS, Beck inventory scale, and caregiver burden scale were re-assessed by the neurologist every 6 months. Physiotherapist and physiatrist in charge of each individualized motor program were not obviously blind to the treatment arm. Motor programs were revised during the follow-up period by the combined re-evaluations performed by the physiotherapist, who re-assessed the patient monthly, and by the physiatrist who visited the patient every 3 months.

Sample size

Sample size was calculated considering as primary endpoint the difference of at least four points in the ALSFRS-R at 12 months, favoring the IER group to the UER. It has been reported that ALS caring neurologists consider of clinically significance a difference of four points in the decline of ALSFRS-R.[11] Assuming an average decline in ALSFRS-R score of 1/month,[12] a difference of four points in 1 year represents a decrease in ALS decline of the 33%.

The null hypothesis was that the mean difference in ALSFRS-R score between the two treatment arms was < 4

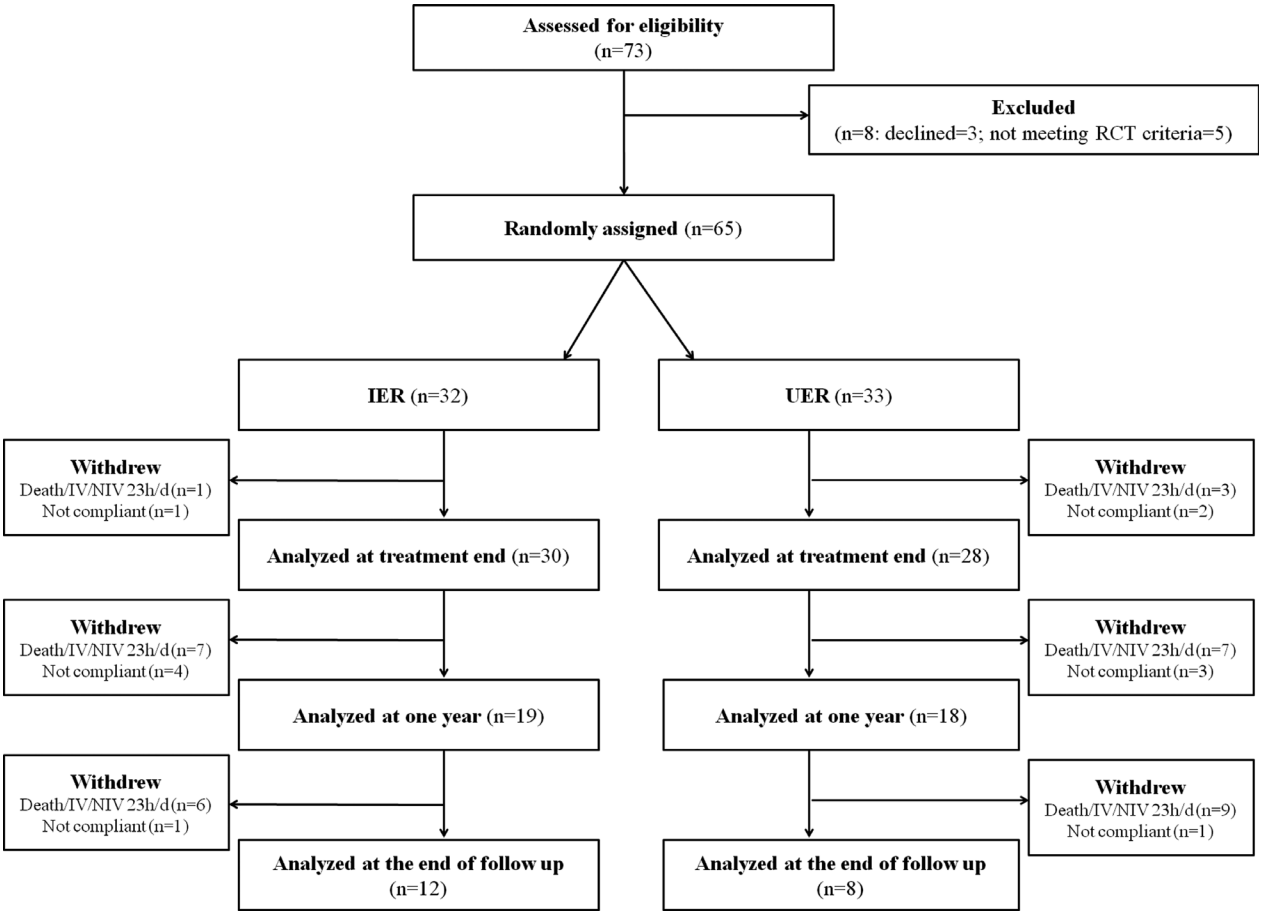

Figure 1. Flow chart of the study.

points at month 12 from baseline. The alternative hypothesis was that IER determined a decrease in ALS decline by at least four points in 12 months.

The study has been designed to reject the null hypothesis with an alpha error of 0.05 and a power of 0.80. For this purpose, a sample of 60 patients randomized in 2 arms would be needed. Considering an average drop out of 5–10%, a recruitment of 63–66 patients would be necessary.

Statistical analysis

The Epidemiological Unit of University of Modena and Reggio Emilia performed all data analysis using STATA 15 software (Stata Inc. 2016, College Station, Texas). Statistical differences between the two treatment arms were computed by *t*-tests or chi-squared test as appropriate.

Multivariable or bivariable conditional logistic regression was used to calculate relative risks.

Survival was calculated from disease onset to death or tracheostomy. Differences in tracheostomy-free survival (Kaplan–Meier method) between the two treatment groups were compared using the log-rank test. Cox's proportional hazard model was used to adjust for any possible unbalanced prognostic factors. Missing data have been handled using the last observation carried forward.

Results

Patients characteristics

Table 2 shows the characteristics of the 65 patients enrolled in the study.

Except for one patient who withdrew during the treatment phase because of an accidental fall, which did not occur during the exercise sessions, all severe adverse events (SAEs) were expected due to ALS course (hospital admission due to gastrostomy, NIV, IV, progressive respiratory insufficiency leading to support or death). During the treatment phase, there were five SAEs (1 fall, 1 tracheostomy, 3 deaths); during the follow-up phase (22 months), 20 patients died and 11 patients underwent tracheostomy.

Table 2. Patients characteristics at baseline.

	IER (n = 32) n (%), mean [SD]	UER (n = 33) n (%), mean [SD]	P value
Sex (male)	26 (81.25)	23 (69.70)	0.280
Onset (spinal)	28 (87.50)	26 (78.79)	0.349
Age at onset (years)	65.14 [9.90]	64.74 [10.10]	0.873
Disease duration at enrollment (months)	15.67 [9.74]	16.64 [8.98]	0.677
ALSFRS-r (total score, points)	39.84 [5.70]	40.15 [5.17]	0.820
Bulbar score (points)	11.16 [1.27]	10.70 [2.42]	0.344
Motor score (points)	17.09 [5.62]	17.084 [4.45]	0.550
Respiratory score (points)	11.59 [0.67]	11.61 [0.79]	0.946
Disease progression rate (points/month)	0.68 [0.49]	0.52 [0.40]	0.142
Forced vital capacity (%)	91.88 [18.98]	90.70 [17.68]	0.796
Riluzole treatment	31 (96.88)	32 (96.97)	0.982

IER, intensive exercise regimen; UER, usual exercise regimen; ALSFRS-R, amyotrophic lateral sclerosis functional rating scale - revised.

Effects of exercise regimen on disease progression

ALSFRS-R at different time points during follow-up period was not significantly different across the two groups (Fig. 2, Table 3).

Next, subscores within ALSFRS-R were analyzed to detect if motor or respiratory domains had benefited more of one regimen over the other (Table 3). No differences in each subscore were found.

There was no advantage in survival for IER group compared to UER (Fig. 3A). Median tracheostomy-free survival from onset was 38 months for patients in IER and 35 months for patients in UER (HR 0.89, 95% CI 0.45–1.78, $P = 0.754$). Multivariable analysis performed with Cox regression model and taking into account age, ALSFRS-R, and FVC at basal evaluation, confirmed the lack of a prognostic role of IER/UER (HR 0.96, 95% CI 0.48–1.91, $P = 0.906$). Similar results were obtained considering the time from onset to PEG or NIV in the two treatments groups (Fig. 3B,C).

Effects of exercise regimen on respiratory function

Respiratory function was assessed by serial measurements of FVC% (Table 4) and deterioration of the sum of respiratory items score on the ALSFRS-R. No significant difference was consistently observed between the two treatment arms at the different time points during the follow-up period.

Effects of exercise regimen on other disease symptoms, fatigue, and quality of life

We did not find differences in quality of life between the two groups, as assessed by ALSAQ40 and McGill scales every 6 months. The score of Beck's Inventory scale for depression assessed every 6 months was equal between the two groups. With regard to Caregiver Burden Index, no substantial discrepancy was noted between the two treatment arms (only at the last observation the difference is near to significance). Finally, FSS score was increased in the IER during the last 12 months of follow-up. (Table 5).

Discussion

Our study demonstrated that there are no major changes in ALS disease progression, as well as in survival and respiratory function, induced by high-frequency motor exercise training of ALS patients.

The role of exercise in ALS has been intensely debated in these years, when epidemiological studies shed different light toward physical activity as an exogenous risk factor for the development of the disease.[13]

Regardless of how exercise might have contributed to degeneration in ALS, some studies showed exercise tolerance is reduced in patients as skeletal muscles' oxygen transport-utilization chain is impaired at different levels.[14] Previous reports attributed the lowered oxygen consumption to deconditioning.[15]

With these premises, the general principles of motor rehabilitation for ALS patients are represented by patient and caregivers' education in safety and fall prevention, strategies for energy conservation, positioning–pressure relief techniques, and prevention of musculoskeletal pain. This translates to environmental modifications, range of motion exercises, functional mobility training, walking programs, cardiopulmonary physical therapy techniques, and strengthening exercise.[16]

Current clinical management for people with ALS includes individualized rehabilitation as part of multidisciplinary care, where physiotherapy and physical exercise are considered useful.[17] When modeling rehabilitation for ALS, two main queries can guide the formulation of a proper program[6]: which type of exercise (stretching, resistance/strengthening, and aerobic/endurance training), and under which regimen, based on intensity, duration, and frequency, is more beneficial to ALS patients. In the majority of tertiary ALS centers in Italy (where the study was carried out), patients usually undergo physiotherapy twice a week, in line with general recommendations for MND patients[18] and with a recent study.[8]

Therefore, we considered this frequency of treatment (twice a week) as the usual regimen (UER).

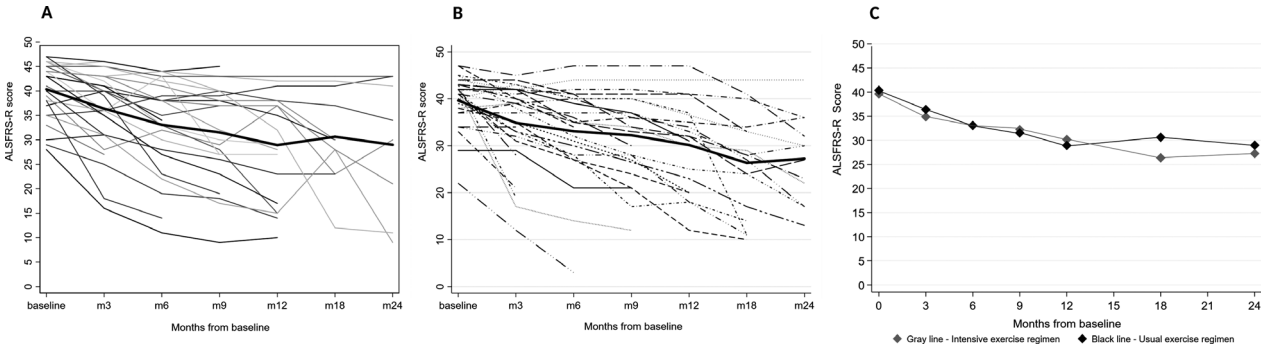

Figure 2. ALSFRS-R total score at different time points in patients treated with IER (A) and in patients treated with UER (B). Mean ALSFRS-R total score at different time points in the two groups (C).

Table 3. Mean total ALSFRS-r, motor items of ALSFRS-r and respiratory items of ALSFRS-r across different time points.

	Time	IER (n = 32) mean, [SD]	UER (n = 33) mean, [SD]	P value
ALSFRS-r total score	3 months (30 vs. 28)	34.87 [8.49]	36.39 [8.01]	0.485
	6 months (25 vs. 26)	33.08 [9.76]	33.08 [9.42]	0.999
	9 months (22 vs. 23)	32.23 [9.15]	31.52 [9.73]	0.804
	12 months (19 vs. 18)	30.16 [9.78]	28.94 [10.87]	0.723
	18 months (17 vs. 11)	26.35 [10.79]	30.64 [9.53]	0.293
	24 months (12 vs. 8)	27.25 [9.20]	29.00 [13.89]	0.737
ALSFRS-r motor items	3 months (30 vs. 28)	13.80 [6.05]	14.93 [6.56]	0.498
	6 months (25 vs. 26)	13.20 [6.30]	13.62 [6.20]	0.813
	9 months (22 vs. 23)	12.59 [6.59]	12.22 [5.79]	0.841
	12 months (19 vs. 18)	11.32 [6.84]	10.89 [6.45]	0.847
	18 months (17 vs. 11)	9.06 [6.61]	10.09 [6.17]	0.682
	24 months (12 vs. 8)	9.58 [6.36]	10.75 [7.80]	0.718
ALSFRS-r respiratory items	3 months (30 vs. 28)	10.73 [2.68]	11.04 [1.57]	0.606
	6 months (25 vs. 26)	10.36 [2.74]	9.81 [2.40]	0.447
	9 months (22 vs. 23)	10.32 [2.80]	9.57 [2.83]	0.375
	12 months (19 vs. 18)	9.58 [3.58]	9.28 [2.95]	0.782
	18 months (17 vs. 11)	9.29 [1.75]	9.29 [3.58]	0.293
	24 months (12 vs. 8)	9.33 [3.77]	10.13 [2.36]	0.605

IER, intensive exercise regimen; UER, usual exercise regimen; ALSFRS-R, amyotrophic lateral sclerosis functional rating scale - revised.

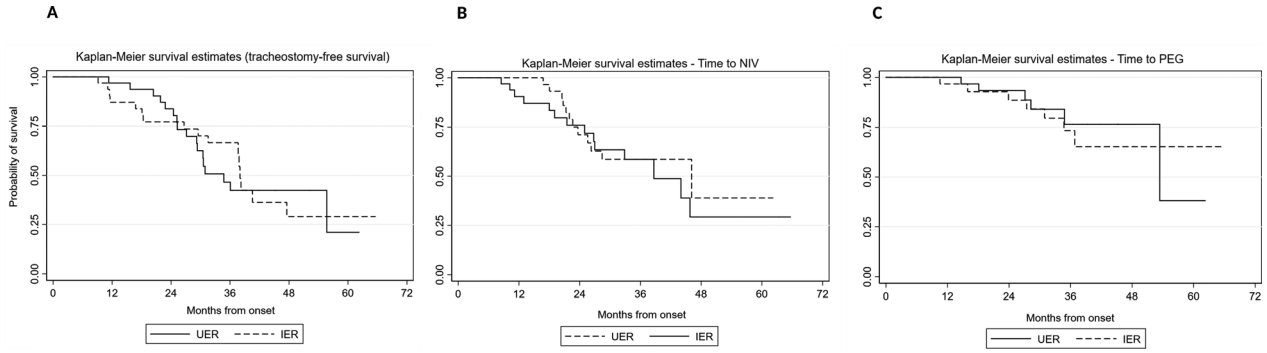

Figure 3. Kaplan–Meyer survival curves from onset of disease to tracheostomy or death (A), to NIV (B), and to PEG (C) in patients treated with IER compared with patients treated with UER.

Table 4. Mean FVC % across different time points in IER and UER treated patients.

Time	IER (n = 32) FVC % mean [SD]	UER (n = 33) FVC % mean [SD]	P value
3 months	73.83 [34.45]	79.30 [35.31]	0.560
6 months	66.24 [44.96]	77.91 [31.82]	0.308
9 months	64.36 [43.94]	64.29 [41.11]	0.995
12 months	80.88 [41.41]	74.47 [35.27]	0.647
18 months	70.79 [42.12]	65.1 [41.64]	0.746
24 months	64.33 [32.28]	65.56 [44.27]	0.942

IER, intensive exercise regimen; UER, usual exercise regimen; FVC, forced vital capacity.

With regard to the protocol choice for the intensive exercise regimen (IER), previous pilot randomized or quasi-randomized clinical trials tested different modalities of exercise even on daily basis,[7,8,19–21] though they were limited by the low number of participants and the short follow-up period.[5,19,22] In order to test a frequency closer to that of these earlier studies, we chose five times per week as the regimen under investigation. More recently in these years other trials investigated which exercise modality is more indicated to ALS patients, expanding the cohort under investigation and the duration of follow-up. One study tested the effect of a daily strictly monitored exercise program, further subdivided into different training modalities (resistive with and without cycloergometer, and stretching) compared to home-based twice weekly passive exercises, finding a reduced decline in global function in the former group as measured by ALSFRS-R but no effects on survival, respiratory function, or QOL were found.[8]

Clawson and colleagues proved there is no harmful effect of thrice weekly resistance or endurance exercise over stretching and range of motion when the decline of ALSFRS-R was compared to data from PRO-ACT database, the major concern being the tolerability to endurance trainings.[7]

Another study[23] evaluated the effects of a mixture of aerobic and muscular strengthening individualized program compared to standard neurorehabilitation protocols for ALS patients, showing better results in terms of muscle power (expressed by the MRC scale), oxygen consumption (measured by VO2submax) and fatigue, not to mention functional independence scale.

Overall, these studies confirm not only passive exercises (range of motion and stretching) but also endurance and

Table 5. Quality of life measures in ALS patients in the two treatment groups as measured by ALSAQ-40 and Mc Gill scales.

	Time	IER (n = 32) mean [SD]	UER (n = 33) mean [SD]	P value
ALSA-Q40	0 months (32 vs. 33)	107.25 [23.12]	105.88 [27.94]	0.830
	6 months (24 vs. 24)	87.79 [39.07]	91.08 [31.44]	0.749
	12 months (15 vs. 12)	76.13 [31.48]	74.92 [41.65]	0.932
	18 months (15 vs. 8)	66.00 [37.10]	92.13 [42.23]	0.140
	24 months (11 vs. 4)	74.64 [42.18]	99.00 [48.75]	0.358
Mc- Gill	0 months (32 vs. 33)	100.09 [24.65]	102.06 [21.97]	0.735
	6 months (24 vs. 25)	86.92 [28.01]	92.92 [29.73]	0.471
	12 months (15 vs. 13)	92.13 [29.70]	90.69 [31.09]	0.901
	18 months (15 vs. 8)	93.93 [31.53]	94.00 [33.50]	0.996
	24 months (11 vs. 4)	92.00 [28.59]	86.00 [54.34]	0.781
Beck Depression Inventory scale	0 months (32 vs. 33)	12.41 [7.22]	11.33 [8.2]	0.578
	6 months (24 vs. 24)	17.17 [12.38]	14.17 [10.19]	0.364
	12 months (14 vs. 11)	15.21 [10.42]	19.18 [11.57]	0.345
	18 months (13 vs. 8)	18.00 [11.09]	15 [10.01]	0.540
	24 months (11 vs. 4)	12.73 [7.40]	14.75 [14.31]	0.720
Caregiver Burden index	0 months (29 vs. 30)	17.41 [15.69]	13.17 [12.75]	0.258
	6 months (20 vs. 21)	24.35 [17.78]	19.14 [16.23]	0.333
	12 months (13 vs. 10)	29.85 [17.26]	27.30 [16.93]	0.727
	18 months (13 vs. 6)	32.92 [20.40]	25.67 [15.27]	0.450
	24 months (10 vs. 4)	28.90 [13.00]	13.25 [14.24]	0.070
Fatigue Severity Scale	0 months (32 vs. 32)	35.63 [15.31]	36.50 [16.53]	0.827
	6 months (24 vs. 24)	41.42 [18.49]	37.38 [18.73]	0.456
	12 months (15 vs. 11)	46.27 [16.25]	36.64 [19.53]	0.183
	18 months (15 vs. 8)	44.13 [15.57]	30.38 [15.58]	0.056
	24 months (11 vs. 4)	52.36 [11.94]	37.25 [24.58]	0.125

Beck Depression Inventory scale, Caregiver Burden Index, and Fatigue Severity Scale in the two treatment groups.
IER, intensive exercise regimen; UER, usual exercise regimen.

moderate load resistive exercises can be applied with benefits and limited side effects (such as cramps or fatigue) to ALS patients.

The reported beneficial effect experienced by the treatment arm in previous studies[8,19–21] is however confounded by the fact that the type, frequency, and intensity of exercise varied between the groups under investigation, making it difficult to understand which aspect was responsible for the benefit.

On the contrary, our study is meant to reflect standard physical rehabilitation programs, where a mixture of exercises is advised, not sticking on one modality over the other,[18] but addressing the specific question on the advised frequency of exercise. To our knowledge, our study is the first RCT to focus on the frequency of a motor program.

The choice of performing all exercise modalities for the same duration, but at different frequencies, in the two treatment arms, removes a potential source of variability not explored in the previous studies. The close monitoring of side effects such as fatigue by continuous re-assessment by physical therapist and questioning by scales allowed us to intervene promptly in re-tailoring motor programs.

No benefit or harm in motor or respiratory function could be observed in the intensive regimen arm of this trial. This on one side reassures about potential risks of repeated exercise in ALS patients. On the other hand, since the relevance of physical therapy is often questioned by patients and in particular at which degree they should insist in doing exercise at local Physical Therapy centres, we provide evidence that twice-a-week programs are not inferior to five times/week programs to maintain a good functional reserve. Besides, quality of life scales were not particularly relevant on one arm compared to the other; it might be speculated the well-being reported in healthy people after exercise may be outbalanced in ALS patients by increased fatigue and disease burden. Unexpectedly, fatigue proved to be increased under IER but only during the second year (of follow-up), that is, after several months from the investigated motor program. This might be explained either by late-onset fatigue due to excess muscle wasting in people under IER, or simply that, given the larger proportion of IER patients still under observation at 24 months, fatigue assessment could be less accurate in UER due to the little amount of patients left in follow-up. The same reasoning may hold for the observation of raised caregiver burden in IER arm at the very end of the follow-up period. Conversely, it is also possible that caregiver burden in relation to IER increases with time and diseases duration.

One limitation of the study is represented by the loss of information during follow-up because of the high number of dropouts due to death or tracheostomy explained by our very long follow-up period. Nevertheless, the long follow-up period is also a strength of this study, as to our knowledge previous investigations on exercise in ALS had a maximum follow-up of 6 months.

Other study limitations to be addressed may come from the selection of the exercises that may be not optimal, and from treatment duration as a 10-week regimen (although followed by continuation by the patient and caregiver at home) may be not sufficient to determine the effect of exercise.

In conclusion, our study showed that twice-a-week sessions composed of a mixture of exercises may have the same beneficial effect on the patient that a high-frequency physical exercise programs, but further studies are warranted to overcome our study limitations.

Acknowledgments

The authors acknowledge ERMOSLA Study Group members (names and affiliations for this group is provided in Appendix S1).

Conflict of Interest

Authors declare no conflict of interest.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. ERMOSLA Study Group Member.

