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ORIGINAL COMMUNICATION

Strictly monitored exercise programs reduce motor deterioration in ALS: preliminary results of a randomized controlled trial

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Abstract The objective of our study was to perform a randomized controlled trial (RCT) aimed to evaluate the effects of three strictly monitored exercise programs (SMEP) compared to "usual care" (UCP) in a cohort of ALS patients. We included patients with definite and probable ALS and disease duration ≤24 months. Patients were randomized to receive a SMEPs or a UCP. SMEPs included three subgroups of treatment: active exercises associated with cycloergometer activity (1A), only active (1B) and passive (1C) exercises, respectively. Moreover, SMEP patients and their caregivers were trained to a daily home-based passive exercise program. The UCP group was treated with passive and stretching exercises twice weekly. The treatment period for both groups was 6 months (T180), and patients were assessed by revised ALS Functional Rating Scale (ALSFRS-R), % Forced Vital Capacity (FVC %), and McGill Quality of Life (MGQoL) questionnaire. ALSFRS-R score was also evaluated at 6 months after the treatment period (T360). Sixty ALS patients were randomly assigned to one of two arms: SMEP Group included 30 patients, ten subjects for each subgroup (1A, 1B, and 1C); 30 patients were included in the UCP Group. At T180 and T360, SMEPs group had significantly higher ALSFRS-R score compared to the UCP group (32.8 ± 6.5 vs 28.7 ± 7.5, $p = 0.0298$; 27.5 ± 7.6 vs 23.3 ± 7.6, $p = 0.0338$, respectively). No effects of SMEPs on survival, respiratory decline and MGQol were found. In conclusion, although no effect on survival was demonstrated, our data suggest that a strictly monitored exercise program may significantly reduce motor deterioration in ALS patients.

Keywords Exercise · Amyotrophic lateral sclerosis · Cycloergometer · ALSFRS-R

Introduction

Amyotrophic lateral sclerosis (ALS) is characterized by the degeneration of upper (corticospinal) and lower (spinal and bulbar) motor neurons, leading to progressive muscle atrophy and paralysis [1]. Patients die on average within 3 years after symptom onset, usually because of respiratory failure. The median age of onset of ALS is 55 years [2]. The incidence of this disorder is 1.5–3.0 per 100,000 person-years in industrialized countries [3]. Muscle weakness and atrophy are considered the cardinal signs of ALS. Initial muscle weakness usually occurs in isolated muscles. This is then followed by progressive and generalized atrophy and weakness associated with functional limitations [4, 5]. There is no cure yet for ALS and the only agent currently licensed for the treatment of ALS is riluzole, an anti-excitotoxic agent that inhibits the release of glutamate, however, that improve the survival of 3–6 months [6–9].

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In the general population, physical exercise exerts a wide range of benefits on health and well-being, controls weight [10], increases muscle strength [11], stimulates the immune system [12], and exerts a positive effect on cardiovascular function [10, 13]. There is also evidence that physical exercise may have a neuroprotective function [14, 15]. Whether physical activity promotes or prevents progression of motor neuron degeneration in ALS is still debated. Vigorous exercise exacerbates the disease progression in ALS animal models and patients [16–18] whereas moderate exercise regimens improve ALS patients' functional scoring and disease symptoms [19, 20]. A recent Cochrane analysis evaluating studies focused on the therapeutic effect of exercise in people with ALS identified only two randomized controlled trials [21], the first one based on a twice-daily exercise program of moderate load, endurance exercise [19] and the second study based on thrice weekly moderate load resistance exercises [20]. Both studies showed a reduction of the motor deterioration evaluated by the revised ALS Functional Rating Scale (ALSFRS-R) compared to the "usual activities" but both studies were too small to elucidate whether exercise is beneficial or harmful in people with ALS.

We conducted a randomized controlled trial (RCT) to evaluate the effects of three strictly monitored exercise programs (SMEP) compared to "usual care" in a cohort of patients with ALS.

Methods

Study design

A 6-month, single-blinded, randomized controlled trial (RCT) followed by a 6-month follow-up was conducted in a dedicated Neuromuscular Clinic in Milan, Italy, the NEMO (NEuroMuscular Omnicomprehensive Center) Clinical Center to evaluate the effects of Strictly Monitored Exercise Programs (SMEPs) compared to a home-based passive exercise program (usual care program, UCP) in a cohort of patients with ALS. The study protocol was approved by the local IRB (Niguarda Ca' Granda Hospital).

Participants

Informed consent according to the declaration of Helsinki was obtained from all participants. Patients fulfilling diagnostic criteria for definite, probable, and probable laboratory-supported ALS with a duration of disease of less than 24 months, mild to moderate disability (documented by satisfactory bulbar and spinal function—minimal score of 3 on ALS-FRS-R for swallowing, cutting food and handling utensils, and walking), a steady treatment regimen with riluzole for at least 3 months and evidence of disease progression over the last 3 months were included in the study. Table 1 describes the inclusion and exclusion criteria of the trial.

Intervention

Eligible participants were randomized to one of the three strictly monitored exercise programs (SMEP-1, -2, -3) or to home-based passive exercise programs (UCP). Randomization to the SMEP cohort (group 1) implied treatment by a trained physiotherapist at the NEMO Center followed by treatment by a trained caregiver at home according to a standardized treatment regimen. All patients of the SMEP groups were treated daily for 2 weeks each month, for 6 consecutive months, according to the exercise program designed for each subgroup. To reduce the risk of drop-out related to the difficulty to reach daily and every week the Centre, we choose this treatment frequency. In particular, three SMEPs were considered:

– *Smep-1* included patients who were treated with an active exercise program combined with cycloergometer activity. The active exercise program was performed at the NEMO Center with the trained physiotherapist and it included active exercises against gravity in six muscle groups in the upper and lower limbs. Only muscles of muscle strength greater than 3 MRC were treated. Each muscle group was subjected to three sets of three reps each. The cycloergometer activity was performed using an electrically braked horizontal cycloergometer for lower limbs associated with a body ergometer for upper limbs (TheraTrainer®) from a sitting position. Training intensity of the treatment program was fixed at 60 % of the patients' maximal power output and maintained for all the treatment period. The duration of each cycle ergometer session was 20 min.
– *Smep-2* included patients who were treated only with an active exercise against gravity in six muscle groups in the upper and lower limbs. Only muscles of muscle strength greater than 3 MRC were treated. Each muscle group was subjected to three sets of three reps each.
– *Smep-3* included patients who were treated with a passive exercise protocol consisting of 20 min of 20 flexion–extension movements per minute in six muscle groups in the upper and lower limbs.

Exercise in all three groups of patients was limited by the subjects' fatigue as evaluated by the Borg perceived scale (7/10) and by the heart rate (75 % of the predicted value).

Group 2 (UCP group) included patients who were randomized to receive a "usual care" program performed only 2 days every week and based on passive exercises,

Table 1 Inclusion and exclusion criteria of the present study

Inclusion criteria
Age between 18 and 75 years
Diagnosis of definite, probable, or probable laboratory-supported ALS
Disease onset ≤24 months
Mild to moderate disability, documented by satisfactory bulbar and spinal function (minimal score of 3 on ALS Functional Rating Scale [ALS-FRS-R] 34 for swallowing, cutting food and handling utensils, and walking)
BMI ≥18
FVC ≥70 % predicted
Exclusion criteria
Serious medical conditions, such as cardiovascular disorders, arterial hypertension, renal or hepatic failure, thyroid disease
Severe mental deterioration
Non compliance with previous treatments
Distance greater than 30 km from study Center (NEMO)

ALSFRS-R revised ALS functional rating scale [24], *BMI* body mass index, *FVC* forced vital capacity

consisting of 20 min of 20 flexion–extension movements per minute in six muscle groups in the upper and lower limbs followed by stretching exercise in the four limbs.

Primary outcome

The primary outcome was the monthly change in global function as measured by the ALSFRS-R scale.

Secondary outcomes

The secondary outcomes were: change in mean ALSFRS-R subscores (bulbar, motor and respiratory function) at T180 and T360; number of death/tracheostomy at 6 and 12 months; change in quality of life subscores.

Assessments

At baseline (T0) and after 2 (T60), 4 (T120), and 6 (T180) months, patients were subjected to the following assessments or procedures:

- ALSFRS-R [22]. This scale is a validated rating instrument to monitor the progression of disability in patients with ALS, evaluating three different domains (bulbar, motor and respiratory function).
- Forced Vital Capacity percentage (FVC %);
- McGill Quality of Life (MGQoL) questionnaire [23]. This scale assesses six domains, including: Single Item, a single question among overall quality of life in the past 2 days; Physical Symptoms or Physical Problems; Psychological Symptoms or Psycological Problems; Physical well-being; existential well-being; support.

Moreover, in all patients only the ALSFRS-R score was also evaluated at 6 months after the treatment period (T360).

Sample size

In order to detect a 10 % difference in the mean monthly ALSFRS-R total score between the SMEP and the UCP groups with a power of 80 % and an alpha risk of 5 %, 60 patients (30 patients in each treatment group) were calculated to be needed in this study. The sample size calculation was based on data obtained from the NEMO ALS-database and specifically on the functional deterioration data in patients with ALS.

Data analysis

All analyses were conducted using SAS 9.3 (SAS Institute, Inc, Cary, NC). Data were reported in the text and in the tables as means and standard deviations for continuous variables and as numbers for non-continuous variables. Statistical differences between the SMEPs and the UCP groups mean data for primary, secondary, and safety outcome measures were compared using t test. Comparisons among the SMEPs subgroups and the UCP group were made using the Wilcoxon rank sum test. Baseline characteristics were analyzed using t test and X^2 test. A p value <0.05 was considered statistically significant and was Bonferroni-adjusted for all tests. We inputted the UCP means for missing data points for both SMEPs and UCP subjects.

Blindness

To preserve blindness, each patient was followed by two physicians: a treating physician, who was aware of the treatment allocation and watched for adverse events; an evaluating physician, who was not aware of treatment allocation and performed all clinical assessments, including

ALS-FRS-R, FVC % and MGQoL. Data analysis was conducted without knowledge of group identities.

Results

Participant numbers and flow chart are shown in Fig. 1. Baseline characteristics are presented in Table 2.

Between April 2009 and April 2012, 62 consecutive patients with probable or definite ALS were assessed for eligibility to the treatment. Two patients were excluded and 60 patients were randomly assigned to SMEP and UCP groups. In detail, 30 ALS patients were assigned to the SMEPs arm (group 1) and the remaining 30 patients were randomized to the UCP arm (group 2). Patients were equally distributed in the two treatment arms, according to their demographic and clinical characteristics (Table 2). Most participants (85 %) were on riluzole therapy at a stable dose (100 mg daily) for 60 days prior to the study and continued medication for the whole treatment period.

During the treatment period, in the SMEP group there were three dropouts, one patient fell accidentally and had a leg fracture, another one did not comply with scheduled visits and the third patient died. One patient in the UCP group died before completion of treatment period. By the end of the follow-up period (T360) three additional patients of the SMEP group died and two required tracheostomy due to respiratory worsening. On the other hand, in the UCP group, two patients died and three required tracheostomy for respiratory failure. None of the deaths or tracheostomy procedures in both groups were related to the treatment, but were attributed to the natural history of the disease.

However, the dropout rates and reasons for dropouts did not differ significantly between the groups (22 of 30 completed in the SMEP group and 25 of 30 in the UCP group, $p = 0.141$) excluding a bias in favor of the SMEP group.

Effects of treatment

Considering all patients recruited in the SMEP group, the mean (standard deviation, SD) ALSFRS-R score at the end of treatment period (T180) was higher compared to those treated in the UCP group (32.8 ± 6.5 vs 28.7 ± 7.5, $p = 0.0298$; Table 3; Fig. 2). Interestingly, the difference remained significant between the two groups (27.5 ± 7.6 vs 23.3 ± 7.6, $p = 0.0338$; Table 3; Fig. 2) also at the end of the follow-up period (T360). Regarding the ALSFRS-R sub-scores (bulbar, motor and respiratory function) we found a significant difference only in the motor domain score at T180 and T360 comparing the SMEP and UCP groups (T180: 14.8 ± 4.3 vs 11.5 ± 5.9, $p = 0.0158$; T360: 11.6 ± 4.8 vs 8.4 ± 6.1, $p = 0.0293$; Fig. 3). Considering the three subgroups in the SMEP group, patients treated with the active exercise program combined with the cycloergometer activity (SMEP-1) were the ones in whom the difference in the ALSFRS-R total score at T180 and T360 compared with the UCP group (Table 3) was more significant. No differences in the ALSFRS-R total score were found comparing the patients of the other two SMEP subgroups and the UCP subjects (Table 3).

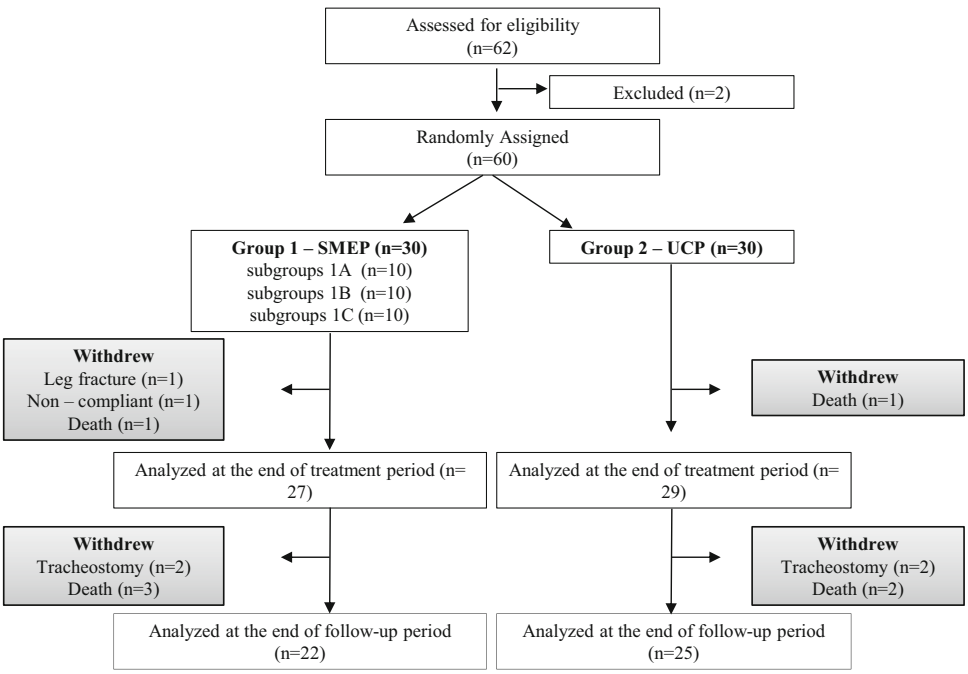

Fig. 1 Random assignments to treatment, withdrawals during the treatment and follow-up periods and completion of the trial. The number of patients who died during the treatment and follow-up phases is also reported

Table 2 Clinical characteristics of recruited patients at baseline between SMEP and UCP groups

	SMEP groups ($N = 30$)	UCP group ($N = 30$)	p
Age	61.1 ± 10.1	60.3 ± 9.9	ns
Sex (male/female)	21/9	17/13	ns
Site of onset (bulbar/spinal)	8/22	10/20	ns
Disease duration (mean ± SD) months	15.2 ± 7.2	13.7 ± 6.1	ns
ALSFRS-R (mean ± SD)	39.1 ± 4.7	38.3 ± 5.1	ns
Bulbar (mean ± SD)	9.5 ± 3.1	9.7 ± 2.8	ns
Motor (mean ± SD)	18.4 ± 3.3	17.3 ± 4.0	ns
Respiratory (mean ± SD)	11.2 ± 1.3	11.3 ± 1.1	ns
% FVC (mean ± SD)	92.5 ± 23.3	93.9 ± 14.7	ns

SMEP strictly monitored exercise program, *UCP* usual care program, *% FVC* % forced vital capacity

Table 3 Mean monthly ALSFRS-r total score among SMEP group and its subgroups and UCP group

	SMEP	p	SMEP-1	p	SMEP-2	P	SMEP-3	p	UCP group
ALSFRS-r total score (T0)	39.1 ± 4.7	ns	41.7 ± 5.6	0.0232*,§	36.9 ± 3.6	ns	38.8 ± 3.6	ns	38.3 ± 5.1
ALSFRS-r total score (T30)	37.0 ± 5.1	ns	38.7 ± 6.4	ns	36.5 ± 3.5	ns	35.9 ± 5.0	ns	38.1 ± 4.3
ALSFRS-r total score (T60)	35.8 ± 5.8	ns	36.8 ± 7.9	ns	35.7 ± 4.7	ns	34.9 ± 5.4	ns	36.6 ± 4.8
ALSFRS-r total score (T90)	35.1 ± 6.2	ns	36.3 ± 8.3	ns	34.6 ± 4.7	ns	34.3 ± 5.3	ns	34.3 ± 6.4
ALSFRS-r total score (T120)	34.7 ± 6.1	ns	35 ± 9.1	ns	34.0 ± 4.6	ns	35.1 ± 3.7	ns	32.7 ± 7.2
ALSFRS-r total score (T150)	33.5 ± 6.2	ns	33.7 ± 9.4	ns	32.8 ± 4.7	ns	34.0 ± 4.5	ns	32.1 ± 7.8
ALSFRS-r total score (T180)	32.8 ± 6.5	0.0298*	33.9 ± 9.6	0.0336*	32.2 ± 5.3	ns	32,2 ± 4,0	ns	28.7 ± 7.5
ALSFRS-r total score (T360)	27.5 ± 7.6	0.0338*	30.5 ± 9.5	0.0345*	24.6 ± 6.7	ns	27.5 ± 5.6	ns	23.3 ± 7.6

ALSFRS-R revised ALS functional rating scale [24], *SMEP* strictly monitored exercise programs, *UCP* usual care program

* Compared to UCP

§ SMEP-1 vs SMEP-2 $p = 0.0137$; SMEP-1 vs SMEP-3 $p = 0.0191$

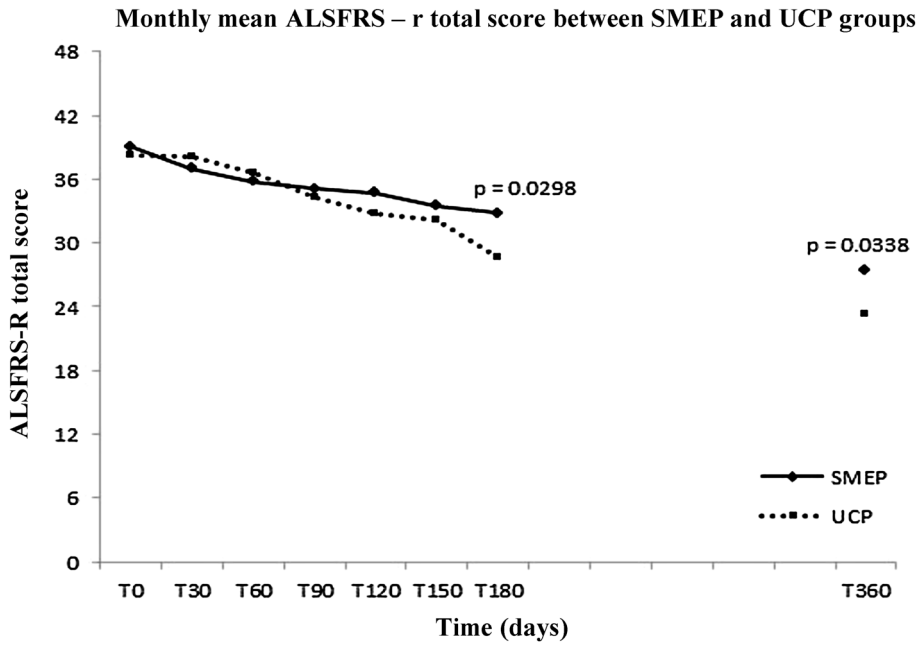

Fig. 2 Monthly mean ALSFRS-R scores over time for the SMEP (*filled diamond*) and UCP (*filled circle*) groups. At T180 and T360, SMEP group had significantly higher ALSFRS-R score compared to the UCP group (32.8 ± 6.5 vs 28.7 ± 7.5, $p = 0.0298$; 27.5 ± 7.6 vs 23.3 ± 7.6, $p = 0.0338$, respectively)

There was no effect of SMEPs on survival and decline of respiratory function (mean FVC %).

In both groups quality of life (MGQoL total score or subscores) was similar at T180, however, in SMEP group the MG-psychological symptom (MG-PsyS) subscore was significantly higher at T180 compared to T0 (Table 4).

Moreover, all patients included in the SMEP group reported an improvement of subjective sense of well-being at the end of every exercise session.

Discussion

Our results demonstrate that a strictly monitored exercise program results in a less significant global function decline in ALS in agreement with previous reports on other exercise programs in ALS patients [19, 20]. ALSFRS-R total scores were maintained both at the end of the protocol and after 6-month follow-up compared to the control group, suggesting that the effects on disease progression could be due both to the frequency and the intensity of the exercise program applied. In this context, even if the number is quite low ($N = 10$ per groups), the subgroup of patients treated with active exercises combined with cycloergometer activity (SMEP-1) showed the higher effect on motor function measured with ALSFRS-R.

Moreover, the delayed effect found at the end of the follow-up period may support the idea of a potential protective effect of a monitored exercise program on disability progression.

Previous studies on the effects of exercise in ALS have yielded conflicting results [25–27]. This could be related to the type, frequency and duration of physical activity and to the heterogeneity of the populations studied where possible confounding factors such as sex, ethnicity, diet, work activities, co-morbidities, etc. may not have been entirely taken into account. Bearing in mind that muscle weakness is very common in people with ALS, it's worthwhile to consider that a weak muscle can be damaged if overworked because it is already functioning close to its maximal limits. Because of this, some experts have discouraged exercise programs for people with ALS. However, if a person with ALS is not active, deconditioning (loss of muscle performance) and weakness from lack of use occur, and these represent an additional detrimental effect which aggravates the ALS-related deconditioning and weakness. If the reduced level of activity persists, many organ systems can be affected and a person with ALS can develop further deconditioning and muscle weakness; muscle and joint tightness may occur leading to contractures (abnormal distortion and shortening of muscles) and pain. Thus, in ALS muscle weakness may worsen if physical activity is avoided, and this, in turn, could lead to cardiovascular deconditioning and disuse weakness, superimposed on the weakness caused by the ALS itself [21]. Our results support the idea that a strictly monitored exercise program might have positive physiological and psychological effects on disuse weakness for people with ALS, especially when implemented before significant muscular atrophy occurs. Moreover, the exercise programs in our study protocol did not have detrimental effects compared to usual care program. Thus, in agreeing with the results of our study a tailored exercise program, according to residual muscle function and based on active and passive exercises combined with cycloergometer activity seems not to be harmful and should be suggested in patients with ALS.

The progressive paralysis in ALS is the result of degeneration and demise of motor neurons [28]. Nevertheless, data from multiple studies suggest that toxicity is non-cell-autonomous, meaning toxicity to motor neurons derives from damage developed within cell types beyond motor neurons [29–31] including skeletal muscle fibers [32–34], fibroblasts [35, 36], and lymphocytes [37]. Several studies have suggested that morphofunctional alterations in skeletal muscle could precede motor neuron degeneration [38–41], suggesting that muscle atrophy in ALS could not be solely due to denervation but could be intrinsic to the muscle fiber. These data support the concept that therapeutic approaches targeted to reverse atrophy and strengthen the muscular activity may prove to be beneficial

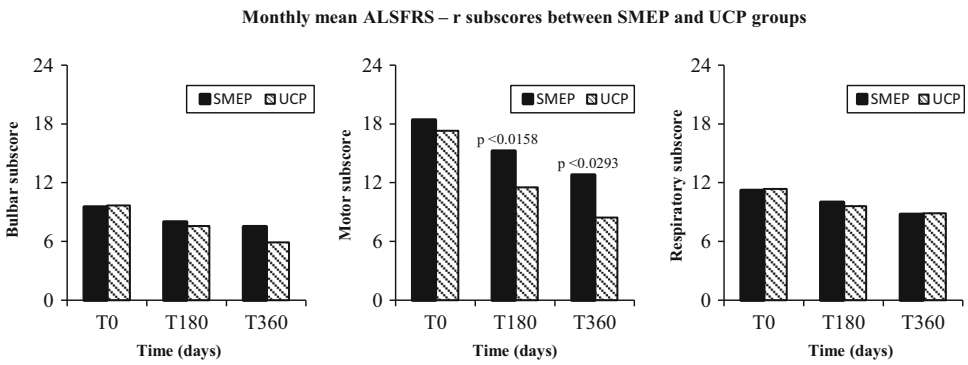

Fig. 3 Mean ALSFRS-r subscores (bulbar, motor and respiratory function) at T0, T180 and T360 in SMEP and UCP groups. At T180 and T360, SMEP group had significantly higher ALSFRS-R motor subscore compared to the UCP group (T180: 14.8 ± 4.3 vs 11.5 ± 5.9, $p = 0.0158$; T360: 11.6 ± 4.8 vs 8.4 ± 6.1, $p = 0.0293$)

Table 4 Clinical and QoL data at the end of the treatment (T180) between SMEP and UCP groups

	T0			T180		
	SMEP groups	UCP group	*p*	SMEP groups	UCP group	*p*
Mean time enrolment to death, months (SD)			ns	10.8 (1.9)	7.9 (3.9)	ns
Mean % FVC (SD)			ns	75.8 (23.6)	66.5 (26.9)	ns
Mean Mc Gill domains (SD)						
MG-SIS	5.0 (3.1)	6.7 (2.6)	ns	5.3 (2.2)	5.0 (3.2)	ns
MG-PhWB	5.7 (2.4)	7.2 (1.9)	ns	5.4 (2.4)	5.0 (2.8)	ns
MG-PhS	14.2 (8.1)	17.5 (7.6)	ns	13.6 (7.5)	10.9 (9.7)	ns
MG-PsyS	18.0 (10.1)	25.1 (8.8)	ns	22.9 (9.7)*	20.1 (14.9)	ns
MG-EWB	44.4 (13.7)	52.6 (8.9)	ns	40.1 (15.2)	44.4 (13.8)	ns
MG-SS	16.1 (4.0)	19.0 (1.7)	0.0031	17.1(3.3)	17.5 (2.5)	ns

% FVC % forced vital capacity, *MG* Mc Gill scale, *MG-SIS* MG single item scale, *MG-PhWB* MG-physical well-being, *MG-PhS* MG-physical symptoms, *MG-PsyS* MG-psychological symptoms, *MG-EWB* MG-existential well-being, *MG-SS* MG-social support

* SMEP groups T0 vs SMEP groups T180 $p = 0.0479$

in this disease. In a previous study, we described that muscular IGF-1 levels were decreased and this was associated to a down-regulation of the expression of activated Akt, suggesting that muscle atrophy was associated in part to intrinsic defects, not associated with myogenin-induced atrophy during denervation [42, 43]. In this context, the beneficial anti-atrophy effects of exercise training might be mediated by inhibiting oxidative stress-induced MuRF1 up-regulation and by preventing MuRF1-mediated degradation of MHC [44].

Despite the beneficial effects of the exercise program described in our cohort no effects of the SMEPs on survival, respiratory function and quality of life compared to the UCP were found. Regarding the lack of effect on QoL or the increment of psychological symptom subscore, it may be that exercise may reduce disease progression, but worsening of motor function occurs anyhow; so that this probably outweighs the patients' perception of QoL. However, all patients included in the SMEP group reported an improvement of subjective sense of well-being at the end of every exercise session as demonstrated by the fact that the subject adherence was generally good, with most patients completing the prescribed exercise sessions.

In addition, although our results are encouraging, there are several limitations to the study. Firstly the number of patients was limited, in particular in the three specific treatment groups ($N = 10$ per groups). Secondly, we did not correlate functional improvement with biological markers of muscle activity, like VEGF expression for instance [45]. The risk of bias in our study needs to be considered, although this was limited due to the study design which included two physicians, the first one who was aware of treatment allocation and watched for adverse events and the second one who was not aware of treatment allocation and performed all clinical assessments.

Finally, our study also demonstrates the feasibility to train caregivers to perform a daily home-based passive exercise program including stretching. This emphasizes the importance and the potentiality to perform a home-based exercise program administered by caregiver regardless of the degree of patient disability.

Conclusions

Despite its limitations, our study supports the idea that physical activity is not a risk factor for ALS and may eventually be protective against the disease [46–49]. ALS care requires an integrated approach in which drugs, nutritional and respiratory support need to be inserted in a strictly monitored physical exercise program, early in the course of the disease. Studies with larger sample sizes are needed to confirm whether physical therapy and, in particular, strictly monitored exercise programs combined with cycloergometer activity can be beneficial in ALS patients.

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Compliance with ethical standards

Conflicts of interest The authors report no conflicts of interest relevant to the manuscript. The authors alone are responsible for the content and writing of the paper.

Ethical standard The study procedures were approved by our Institutional Review Board according to ethical principles and guidelines for the protection of human subjects for research.

References

1. Brooks BR, Sanjak M, Belden D, Juhasz-Poscine K, Waclawik A (2000) Natural history of amyotrophic lateral sclerosis. In: Brown RHJ, Meininger V, Swash M (eds) Amyotrophic lateral sclerosis. Dunitz, London, pp 31–58
2. Pasinelli P, Brown RH (2006) Molecular biology of amyotrophic lateral sclerosis: insights from genetics. Nat Rev Neurosci 7:710–723
3. Logroscino G, Traynor BJ, Hardiman O, Chio' A, Couratier P, Mitchell JD, Swingler RJ, Beghi E (2008) Descriptive epidemiology of amyotrophic lateral sclerosis: new evidence and unsolved issues. J Neurol Neurosurg Psychiatry 79:6–11
4. Wijesekera LC, Leigh PN (2009) Amyotrophic lateral sclerosis. Orphanet J Rare Dis 4:3
5. Swash M, Desai J (2000) Motor neuron disease: classification and nomenclature. Amyotroph Lateral Scler Other Motor Neuron Disord 1:105–112
6. Cleveland DW, Rothstein JD (2001) From Charcot to Lou Gehrig: deciphering selective motor neuron death in ALS. Nat Rev Neurosci 2:806–819
7. Sreedharan J, Brown RH Jr (2013) Amyotrophic lateral sclerosis: problems and prospects. Ann Neurol 74:309–316. doi:10.1002/ana.24012.Review
8. Carter GT, Joyce NC, Abresch AL, Smith AE, VandeKeift GK (2012) Using palliative care in progressive neuromuscular disease to maximize quality of life. Phys Med Rehabil Clin N Am 23:903–909. doi:10.1016/j.pmr.2012.08.002 **(epub 2012 Oct 17 review)**
9. Prell T, Grosskreutz J (2013) The involvement of the cerebellum in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener 14:507–515. doi:10.3109/21678421.2013.812661
10. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, Nieman DC, Swain DP, American College of Sports Medicine (2011) American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc 43:1334–1359
11. Serfass RC, Gerberich SG (1984) Exercise for optimal health: strategies and motivational considerations. Prev Med 13:79–99
12. American College of Sports Medicine, Chodzko-Zajko WJ, Proctor DN, Fiatarone Singh MA, Minson CT, Nigg CR, Salem GJ, Skinner JS (2009) American College of Sports Medicine position stand. Exercise and physical activity for older adults. Med Sci Sports Exerc 41:1510–1530
13. Seron P, Lanas F, Pardo Hernandez H, Bonfill Cosp X (2014) Exercise for people with high cardiovascular risk. Cochrane Database Syst Rev 13(8):CD009387
14. Svensson M, Lexell J, Deierborg T (2014) Effects of physical exercise on neuroinflammation, neuroplasticity, neurodegeneration, and behavior: what we can learn from animal models in clinical settings. Neurorehabil Neural Repair 29:577–589. doi:10.1177/1545968314562108 **epub 2014 Dec 19**
15. Van Praag H, Fleshner M, Schwartz MW, Mattson MP (2014) Exercise, energy intake, glucose homeostasis, and the brain. J Neurosci 12(34):15139–15149
16. Mahoney DJ, Rodriguez C, Devries M, Yasuda N, Tarnopolsky MA (2004) Effects of high-intensity endurance exercise training in the G93A mouse model of amyotrophic lateral sclerosis. Muscle Nerve 29:656–662
17. Scarmeas N, Shih T, Stern Y, Ottman R, Rowland LP (2002) Premorbid weight, body mass, and varsity athletics in ALS. Neurology 59:773–775
18. Chio A, Benzi G, Dossena M, Mutani R, Mora G (2005) Severely increased risk of amyotrophic lateral sclerosis among Italian professional football players. Brain 128:472–476
19. Drory VE, Goltsman E, Reznik JG, Mosek A, Korczyn AD (2001) The value of muscle exercise in patients with amyotrophic lateral sclerosis. J Neurol Sci 191:133–137
20. Dal Bello-Haas VD, Florence JM, Kloos AD, Scheirbecker J, Lopate G, Hayes SM, Pioro EP, Mitsumoto H (2007) A randomized controlled trial of resistance exercise in individuals with ALS. Neurology 68:2003–2007
21. Dal Bello-Haas V, Florence JM (2013) Therapeutic exercise for people with amyotrophic lateral sclerosis or motor neuron disease. Cochrane Database Syst Rev 5:CD005229
22. Cedarbaum JM, Stambler N, Malta E, Fuller C, Hilt D, Thurmond B, Nakanishi A (1999) The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). J Neurol Sci 169:13–21
23. Cohen SR, Mount BM, Strobel MG, Bui F (1995) The McGill Quality of Life Questionnaire: a measure of quality of life appropriate for people with advanced disease. A preliminary study of validity and acceptability. Palliat Med 9:207–219
24. Franchignoni F, Mora G, Giordano A, Volanti P, Chiò A (2013) Evidence of multidimensionality in the ALSFRS-R Scale: a critical appraisal on its measurement properties using Rasch analysis. J Neurol Neurosurg Psychiatry 84:1340–1345
25. Munsat TL (1980) Commentary. In: Mulder DW (ed) The diagnosis and treatment of amyotrophic lateral sclerosis. Houghton Mifflin, Boston, pp 214–215
26. Bennett RL, Knowlton GC (1958) Overwork weakness in partially denervated skeletal muscle. Clin Orthop 12:711–715
27. Johnson EW, Braddom R (1971) Overwork weakness in facioscapulohumeral muscular dystrophy. Arch Phys Med Rehabil 52:333–336
28. Rowland LP, Shneider NA (2001) Amyotrophic lateral sclerosis. N Engl J Med 344:1688–1700
29. Fuchs CS, Giovannucci EL, Colditz GA, Hunter DJ, Speizer FE, Willett WC (1994) A prospective study of family history and the risk of colorectal cancer. N Engl J Med 331:1669–1674
30. Boillee S, Van de Velde C, Cleveland DW (2006) ALS: a disease of motor neurons and their non neuronal neighbors. Neuron 52:39–59
31. Ilieva H, Polymenidou M, Cleveland DW (2009) Non-cell autonomous toxicity in neurodegenerative disorders: ALS and beyond. J Cell Biol 187:761–772
32. Wiedemann FR, Winkler K, Kuznetsov AV, Bartels C, Vielhaber S, Feistner H, Kunz WS (1998) Impairment of mitochondrial function in skeletal muscle of patients with amyotrophic lateral sclerosis. J Neurol Sci 156:65–72
33. Krasnianski A, Deschauer M, Neudecker S, Gellerich FN, Müller T, Schoser BG, Krasnianski M, Zierz S (2005) Mitochondrial changes in skeletal muscle in amyotrophic lateral sclerosis and other neurogenic atrophies. Brain 128:1870–1876
34. Dupuis L, Gonzalez de Aguilar JL, Echaniz-Laguna A, Loeffler JP (2006) Mitochondrial dysfunction in amyotrophic lateral sclerosis also affects skeletal muscle. Muscle Nerve 34:253–254
35. Aguirre T, Van Den Bosch L, Goetschalckx K, Tilkin P, Mathijs G, Cassiman JJ, Robberecht W (1998) Increased sensitivity of fibroblasts from amyotrophic lateral sclerosis patients to oxidative stress. Ann Neurol 43:452–457
36. McEachern G, Kassovska-Bratinova S, Raha S, Tarnopolsky MA, Turnbull J, Bourgeois J, Robinson B (2000) Manganese

superoxide dismutase levels are elevated in a proportion of amyotrophic lateral sclerosis patient cell lines. Biochem Biophys Res Commun 273:359–363
37. Cova E, Cereda C, Galli A, Curti D, Finotti C, Di Poto C, Corato M, Mazzini G, Ceroni M (2006) Modified expression of Bcl-2 and SOD1 proteins in lymphocytes from sporadic ALS patients. Neurosci Lett 399:186–190
38. Dobrowolny G, Aucello M, Rizzuto E, Beccafico S, Mammucari C, Boncompagni S, Belia S, Wannenes F, Nicoletti C, Del Prete Z et al (2008) Skeletal muscle is a primary target of SOD1G93A-mediated toxicity. Cell Metab 8:425–436
39. Wong M, Martin LJ (2010) Skeletal muscle-restricted expression of human SOD1 causes motor neuron degeneration in transgenic mice. Hum Mol Genet 19:2284–2302
40. Dupuis L, Gonzalez de Aguilar JL, Echaniz-Laguna A, Eschbach J, Rene F, Oudart H, Halter B, Huze C, Schaeffer L, Bouillaud F et al (2009) Muscle mitochondrial uncoupling dismantles neuromuscular junction and triggers distal degeneration of motor neurons. PLoS One 4:e5390
41. Zhou J, Yi J, Fu R, Liu E, Siddique T, Ríos E, Deng HX (2010) Hyperactive intracellular calcium signaling associated with localized mitochondrial defects in skeletal muscle of an animal model of amyotrophic lateral sclerosis. J Biol Chem 285:705–712
42. Léger B, Vergani L, Sorarù G, Hespel P, Derave W, Gobelet C, D'Ascenzio C, Angelini C, Russell AP (2006) Human skeletal muscle atrophy in amyotrophic lateral sclerosis reveals a reduction in Akt and an increase in atrogin-1. FASEB J 20:583–585
43. Lunetta C, Serafini M, Prelle A, Magni P, Dozio E, Ruscica M, Sassone J, Colciago C, Moggio M, Corbo M, Silani V (2012) Impaired expression of insulin-like growth factor-1 system in skeletal muscle of amyotrophic lateral sclerosis patients. Muscle Nerve 45:200–208
44. Chen GQ, Mou CY, Yang YQ, Wang S, Zhao ZW (2011) Exercise training has beneficial anti-atrophy effects by inhibiting oxidative stress-induced MuRF1 up regulation in rats with diabetes. Life Sci 89:44–49
45. Carilho R, de Carvalho M, Swash M, Pinto S, Pinto A, Costa J (2014) Vascular endothelial growth factor and amyotrophic lateral sclerosis: the interplay with exercise and noninvasive ventilation. Muscle Nerve 49:545–550
46. Pupillo E, Messina P, Giussani G et al (2014) Physical activity and amyotrophic lateral sclerosis: a European population-based case-control study. Ann Neurol. 75:708–716
47. Veldink JH, Bar PR, Joosten EAJ, Otten M, Wokke JH, van den Berg LH (2003) Sexual differences in onset of disease and response to exercise in a transgenic model of ALS. Neuromusc Disord 13:737–743
48. Liebetanz D, Hagemann K, von Lewinski F, Kahler E, Paulus W (2004) Extensive exercise is not harmful in amyotrophic lateral sclerosis. Eur J Neurosci 20:3115–3120
49. Veldink JH, Kalmijn S, Groeneveld GJ, Titulaer MJ, Wokke JH, van den Berg LH (2005) Physical activity and the association with sporadic ALS. Neurology 64:241–245