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ORIGINAL ARTICLE

A randomized, placebo-controlled trial of memantine for functional disability in amyotrophic lateral sclerosis

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Abstract

Our objective is to describe the results of a phase II/III, 12-months, double-blinded, single-centre, randomized, parallel (1:1), clinical trial performed to evaluate the efficacy and safety of memantine in ALS. Patients with probable or definite ALS of less than 36 months disease duration and progression over a one-month lead-in period were randomly assigned to placebo or memantine at 20 mg/day. The primary endpoint was 12-months ALSFRS decline. Forced vital capacity, manual muscle testing, visual analogue scale, quality of life, motor unit number estimation and neurophysiological index were the secondary endpoints. The number of patients included was based on the assumption of a 50% change in the ALSFRS decline. Safety and adverse events were evaluated. Sixty-three patients were included in the trial. Memantine did not show more adverse events or laboratory changes than placebo. Primary and secondary outcomes were not different between groups by intention-to-treat and per-protocol analysis. The most sensitive measurements were neurophysiological, which declined linearly over time. In conclusion, the results of this study show that memantine is well tolerated and safe in ALS patients. We did not observe any evidence of efficacy for memantine but we cannot exclude a positive outcome on survival.

Key words: *Amyotrophic lateral sclerosis, clinical trial, memantine, neurophysiological index, progression*

Introduction

There is strong evidence that glutamate-mediated toxicity is associated with neuron degeneration in ALS and other neurodegenerative disorders (1). Cultured motor neurons are vulnerable to glutamate toxicity by activation of both NMDA and non-NMDA receptors (2). Riluzole, a glutamate antagonist, is the only pharmacological intervention that has been shown to improve the survival of ALS patients in randomized controlled clinical trials (3). Memantine is a novel, safe and efficacious class of Alzheimer's disease medication (4) acting on the glutamatergic system by modulating NMDA glutamate receptors. It is a moderate-affinity voltage-dependent non-competitive antagonist at glutamatergic NMDA receptors, which preserves the physiological function of the receptor. Consequently, chronic and low-level activation of NMDA receptors is modulated, but functional NMDA receptor activation is preserved (5).

Memantine prolongs survival in an ALS mouse model (G93A) (2,6), but its efficacy in human ALS is largely unknown. Therefore, we evaluated the efficacy and safety of memantine in ALS patients enrolled in a phase II/III, 12-months, double-blinded, single-centre, randomized, parallel, clinical trial.

Methods

This was an academic study conducted in our department and registered in clinicaltrials.gov. (NCT00353665).

Patients

Eligible patients were aged 18–75 years and had clinically probable, probable-laboratory supported or definite ALS disease, as defined in the revised El Escorial criteria (7), with disease duration of less than 36 months at study entry. Patients were required to have a forced vital capacity higher than 60% of the predicted value, functional rating scale (ALSFRS) (8) between 25 and 38 and abductor digitimi minimi muscle (ADM) contraction force

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>2 on the MRC scale in at least one hand (to permit neurophysiological assessment during the trial period). We used these inclusion criteria with the aim of recruiting patients who were not severely disabled, as functional improvement is less likely to occur in severely affected ALS patients.

All patients were followed at least one month before entry (lead-in observational period). During this period, riluzole 50 mg b.i.d. was prescribed (if not already on riluzole), patients underwent laboratory monitoring, and capability to adhere to the study protocol was evaluated. To enhance the study population, only patients who showed ALSFRS decline of at least 1 point during this lead-in observational period were included, because of the higher likelihood to show statistical differences regarding progression in ALS patients with clear signs of progression in a short period (9).

Patients were excluded if they had signs of polyneuropathy or conduction block on the nerve conduction studies; other coincident neurological disease; clinical signs of dementia or a minimal mental state <27; uncompensated medical illness; psychiatric disease; laboratory abnormalities consistent with paraproteinaemia, thyroid or liver dysfunction, HIV infection, diabetes or cancer; ECG abnormalities; tracheostomy; gastrostomy; previous participation in other trial; breast feeding; pregnancy or inadequate methods of contraception.

All eligible patients gave written informed consent to participate in this study, which was approved by the hospital ethics committee.

Study design and interventions

The design was a 12-month, randomized, placebo-controlled, double-blind, parallel study.

Randomization was independently performed by the clinical research unit of our department, although a computer-generated list and randomization codes were kept blinded to the study investigators and statisticians. Stratification by region of onset (limb vs. bulbar) within each treatment arm was undertaken, and a block of 4 was used in each stratum. Patients were assigned (ratio of 1:1) to placebo or memantine. All patients were treated with riluzole 50 mg b.i.d.

Memantine was titrated in 5-mg weekly increments from a starting dose of 5 mg i.d. to 10 mg b.i.d. Masked study medication was supplied for dispensation in blister packs at each visit. Drug and placebo tablets were visually identical.

Sample size and outcome measurements

The primary outcome was change in the ALSFRS (40-points rating scale) from baseline to 12 months.

Assuming a hypothetical effect size of 50%, a sample size of at least 30 patients in each treatment group provided a 80% power at a two-sided alpha level of .05, for change from baseline to 12 months in ALS-FRS, as extrapolated from a group of ALS patients with clear signs of progression in a short period of lead-in (9).

The secondary efficacy outcomes were: predicted value of forced vital capacity; manual muscle testing (32 muscle groups as classified on the MRC scale, maximal score 160); patient 100-mm visual analogue scale (for fasciculations, cramps, fatigue and stiffness); medical 100-mm visual analogue scale (global: worse, stable, improved); quality of life (SF-36); motor unit number estimation of both ADM (incremental technique) (10) and neurophysiological index (NI) of both ADM (10). For the neurophysiological measurements the mean value from both hands was calculated and its value used in the analysis.

Participants had seven in-person visits scheduled at screening, entry, months 1, 3, 6, 9 and 12.

All outcome measurements were collected at screening, baseline, 3, 6, 9 and 12 months, except for FVC and neurophysiological measurements which were recorded at entry, 6 and 12 months.

Safety was evaluated by assessment of laboratory tests data for complete blood count, basic chemistry panel, liver function testing and creatine kinase (CK) carried out at each visit, and by reporting of adverse events (standardized safety questionnaire and spontaneous reporting by the patients).

We defined compliance as patient consuming >80% of prescribed medication.

Statistical analysis

The demographic characteristics between the two groups were compared by a Mann-Whitney or χ^2 test as appropriate. In accordance with the intention-to-treat principle, all randomized treated patients were included in the primary statistical analysis using the last observation carried forward. Per-protocol analysis was additionally performed. Analysis of the primary and secondary outcome variables used a mixed model analysis of variance. Safety comparisons between both arms were carried out with two-sided χ^2 or Fisher's exact test.

Results

From July 2005 to June 2007, and according to our inclusion and exclusion criteria, 63 consecutive patients were recruited in our centre (Figure 1) and were randomized to memantine or placebo. The last observation was in July 2008. By pills count, the proportion of patients who met the definition of compliance was 100% for those who finished the trial.

Baseline characteristics (Table I) were similar in both treatment groups.

Thirteen patients prematurely discontinued the study, five in the memantine and eight in the placebo arm. The major reason for study withdrawal was death related to disease progression (four in the

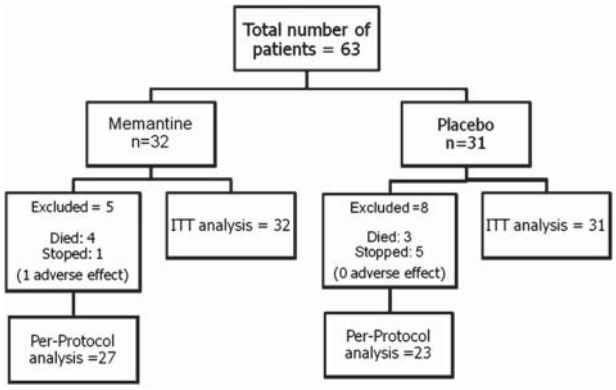

Figure 1. Flowchart of included patients.

active group and three in the placebo group, $p = 0.29$). In the placebo group two were lost to follow-up, two decided to buy the active drug and one decided to stop the medication in spite of non-relevant adverse effects. In the memantine group, one male patient had toxic hepatic reaction and stopped his participation in the trial. This patient had a previous history of hepatitis B infection 35 years earlier, with no symptoms and normal enzymes at trial entry. After interruption of both riluzole and memantine the liver function normalized.

Two patients, one in each treatment group, did not tolerate riluzole (gastric symptoms), which was discontinued, but both remained in the trial. Four out of the six patients of the placebo group and the single patient in the active group who interrupted the trial agreed to be evaluated regularly according to our protocol. The memantine dose was not decreased in any patient.

There was no significant difference between memantine and placebo groups in ALSFRS change from baseline to the end of this trial. Secondary objective efficacy outcomes (MRC score, FVC, MUNE, NI and SF-36 decline over 12 months) were also not different between treatment groups. Table II summarizes these results. Interim analysis at 3, 6 and 9 months also failed to detect any significant difference. Medical (global) and patient subjective evaluation (for fasciculations, cramps, fatigue and stiffness) did not differ between groups. At the end of the trial, 11.5% of memantine treated patients and 18.2% of placebo treated patients underwent percutaneous endoscopic gastrostomy (PEG) placement ($p = 0.69$); 48.3% in the memantine arm needed non-invasive ventilation (NIV) compared with 45.5% in the placebo arm ($p = 0.83$).

Adverse events (AEs) are summarized in Table III. There were no significant differences in the number of patients reporting AEs between the placebo and the memantine group, except for an increased incidence of diarrhoea and other events in the placebo arm (Table III). During the trial three patients were hospitalized due to respiratory infections (one in the memantine arm and two in the placebo arm) and one other patient in the active arm was hospitalized due to cholecystitis. All the patients hospitalized survived the acute episode and were kept in the trial.

Blood counts, CK level, glycaemia and tests of blood chemistry, renal function, and liver function did not differ between treatment groups before randomization. The percentage of patients who developed abnormalities in laboratory safety studies was similar between groups.

Discussion

The results of this study show that memantine is well tolerated and safe in ALS patients. None of the

Table I. Baseline features.

	Memantine	Placebo	Total	*p*
Gender				
Men	21 (65.6%)	21 (67.7%)	42 (66.7%)	0.86
Women	11 (34.4%)	10 (32.3%)	21 (33.3%)	
Age (mean ± standard deviation)	58.9 ± 9.6	58.3 ± 10.0	58.6 ± 9.7	0.86
Disease duration (mean ± standard deviation) (months)	9.3 ± 4.7	9.7 ± 6.6	9.5 ± 5.7	0.77
Body mass index (mean ± standard deviation) 24.8 ± 3.5	25.2 ± 3.5	24.8 ± 3.5	25.0 ± 3.5	0.79
Bulbar onset	8	5	13	0.38
Spinal onset	24	26	50	0.38
ALSFRS (mean ± standard deviation)	33.2 ± 3.4	32.0 ± 4.0	32.6 ± 3.7	0.81
MRC score (mean ± standard deviation)	143.1 ± 12.5	141.3 ± 13.1	142.6 ± 12.0	0.86
FVC (mean ± standard deviation) (% of predicted)	96.1 ± 15.0	92.8 ± 15.3	94.5 ± 15.1	0.26
PEG	0 (0%)	1 (3.2%)	1 (1.6%)	0.49
NIV	2 (6.3%)	0 (0%)	2 (3.2 %)	0.39
MUNE (mean ± standard deviation)	51.6 ± 34.5	38.5 ± 32.7	45.1 ± 34.0	0.08
NI (mean ± standard deviation)	2.4 ± 1.5	2.2 ± 1.4	2.3 ± 1.4	0.52
SF-36 (mean ± standard deviation)	49.9 ± 16.4	49.0 ± 15.1	49.5 ± 15.6	0.91

ALSFRS: functional scale; MRC score: muscular strength as evaluated by MRC scale (score from 0 to 160); FVC: forced vital capacity; PEG: percutaneous endoscopic gastrostomy; NIV: non-invasive ventilation; MUNE: motor unit number estimation; NI: neurophysiological index. *p*-values as obtained by the Mann-Whitney or the χ^2 test as appropriate.

Table II. Treatment effects (see Figure 1).

Outcome measure	Memantine at entry	Memantine at 12 months	Placebo at entry	Placebo at 12 months	*p*-value ITT analysis	*p*-value PP analysis
ALSFRS*	33.2 ± 3.4	20.2 ± 6.9	32.0 ± 4.0	20.6 ± 9.7	0.53	0.46
MRC Score*	143.1 ± 12.5	110.0 ± 26.1	141.3 ± 13.1	105.7 ± 42.4	0.43	0.37
FVC**	96.0 ± 15.3	64.8 ± 27.1	92.7 ± 15.5	79.4 ± 23.9	0.20	0.22
MUNE***	52.2 ± 34.9	19.8 ± 23.5	37.2 ± 32.4	11.1 ± 14.8	0.31	0.13
NI***	2.4 ± 1.5	1.2 ± 0.6	2.1 ± 1.4	1.2 ± 0.8	0.51	0.26
SF-36*	49.9 ± 16.4	37.3 ± 10.9	49.0 ± 15.1	40.7 ± 16.8	0.44	0.44

ALSFRS: functional scale; MRC score: muscular strength as evaluated by MRC scale (score from 0 to 160); FVC: forced vital capacity; MUNE: motor unit number estimation; NI: neurophysiological index; ITT: intention-to-treat analysis; PP: per-protocol analysis.
p-value given by applying mixed model analysis of variance.
*Data from all patients (see Figure 1).
**21 patients in the active group and 17 in the placebo group were evaluated at 12 months.
***23 patients in the active group and 21 in the placebo group were evaluated at 12 months.

serious adverse effects was judged to be related to the study drug. Concerning the patient with a previous hepatitis B infection, but symptomatic hepatic necrosis after trial entry, we believe that the most probable cause was riluzole medication, as reported elsewhere (11).

Although memantine was well tolerated, no therapeutic benefit in patients with ALS was demonstrated. Neither the primary outcome measure nor the secondary outcome measures showed any evidence of efficacy. In the placebo group FVC declined less than expected in ALS (1.19%/month) (12,13) and was lower than in the memantine group (2.71%/month). This difference may be accounted for by the observation that fast progressors could not perform FVC measurement at the end of the trial due to very poor respiratory function. That a similar number of patients were adapted to NIV in both arms supports the conjecture that the difference in the rate of decline in FVC was not clinically relevant. ALSFRS decreased 3.27%/month and 2.97%/month in memantine and placebo arms, respectively, showing that the patients had the expected rate of clinical progression (10,12). Neurophysiological measurements changed to the greatest degree, as previously noted (10,12). MUNE changed 5.17%/month and 5.85%/month, and NI 4.17%/month and 3.58%/month in memantine and placebo arms, respectively.

Riluzole, a glutamate-releasing antagonist is the only disease-modifying drug approved for ALS (3). However, riluzole has properties other than those related to glutamate metabolism. In particular, riluzole inactivates voltage-dependent sodium channels and activates a G-protein- dependent signal transduction process, which can be relevant to its neuroprotective action (13). A number of other trials with anti-glutamatergic drugs have been negative in ALS (14) including a large topiramate trial. Topiramate has anti-excitoxic properties, as it diminishes glutamate release from neurons and antagonizes kainate activation of the AMPA glutamatergic excitatory amino acid receptor (15). It seems that either NMDA or AMPA modulation is insufficient to attenuate the progressive loss of lower motor neurons.

Table III. Adverse events.

	Total occurrence *n* (%)	Memantine *n* (%)	Placebo *n* (%)	*p*-values
Constipation	35 (55.6%)	20 (62.5%)	15 (48.4%)	0.26
Insomnia	34 (54%)	17 (53.1%)	17 (54.8%)	0.89
Falls	30 (47.6%)	18 (56.3%)	12 (38.7%)	0.16
Dizziness	24 (38.1%)	12 (37.5%)	12 (38.7%)	0.92
Anxiety	16 (25.4%)	6 (18.8%)	10 (32.3%)	0.22
Headaches	16 (25.4%)	6 (18.8%)	10 (32.3%)	0.22
Cough	16 (25.4%)	5 (15.6%)	11 (35.5%)	0.07
Urinary symptoms	12 (19.0%)	6 (18.8%)	6 (19.4%)	0.95
Diarrhoea	7 (11.1%)	1 (3.1%)	6 (19.4%)	0.04
Others	30 (47.6%)	11 (34.4%)	19 (61.3%)	0.03
Gastrointestinal symptoms	17 (27%)	5 (15.6%)	12 (38.7%)	–
Depression	3 (4.8%)	2 (6.3%)	1 (3.2%)	–
Cognitive symptoms	2 (3.2%)	1 (3.1%)	1 (3.2%)	–
Leg pain	2 (3.2%)	0 (0%)	2 (6.5%)	–
Bone fracture	2 (3.2%)	2 (6.3%)	0 (0%)	–
Sensory symptoms	2 (3.2%)	0 (0%)	2 (6.5%)	–
Meaningful increased liver enzymes	1 (1.6%)	1 (3.1%)	0 (0%)	–
Meaningful increased glycaemia	1 (1.6%)	0 (0%)	1 (3.2%)	–

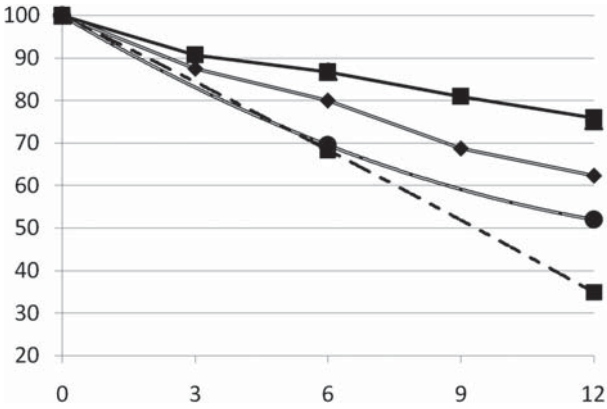

Figure 2. Progression of the outcome measures over the trial period. ALSFRS: functional scale (diamond); MRC score (squares): strength score using MRC scale (from 0 to 160); FVC (diamond): forced vital capacity (predicted value); NI: neurophysiological index (round symbol); MUNE: motor unit number estimation, incremental technique (square with dashed line). The lines of MRC score and FVC are superimposed. Y-axis: the percentage of change (at entry all measures were normalized to 100%); X-axis: the time of evaluation, 0, 3, 6, 12 moths for ALSFRS; MRC score, and 0, 6, 12 months for FVC, MUNE and NI.

In our trial the relevant measurements tended to decline linearly over time (Figure 2). As demonstrated elsewhere, the NI, which is simple, rapid and well tolerated to perform, is an attractive measurement as it provides a direct measure of the number of functional motor units, and changes strikingly over disease progression.

Our study was an exploratory trial including a small number of patients. The failure of this study to show a change in the functional rate of decline does not preclude the possibility that memantine may have an effect on survival, for which this study was underpowered.

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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