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ORIGINAL COMMUNICATION

A randomized clinical trial of lithium in multiple system atrophy

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Abstract The aim of our study was to test the safety and tolerability of lithium in multiple system atrophy (MSA). The study was randomized, placebo-controlled, and double-blind. The primary endpoint of the study was safety and tolerability. An interim analysis, performed 1 year after the first patient was randomized, showed a higher proportion of trial abandon ($P < 0.01$) and a higher number of adverse events ($P < 0.02$) in the lithium group. The trial was stopped by the Data Monitoring Committee. Overall, lithium was not well tolerated, and we do not encourage future studies with lithium in MSA patients.

Keywords Lithium · Multiple system atrophy · Clinical trial · Safety · Phase II

Introduction

Multiple system atrophy (MSA) is a rare, sporadic, progressive neurodegenerative disease presenting with parkinsonian features, cerebellar ataxia, autonomic failure, and corticospinal disorders [1]. The pathological hallmark of the disease is the formation of oligodendrocyte cytoplasmic inclusions of fibrillized alpha-synuclein, and the subsequent induction of apoptosis. It was recently demonstrated that lithium is able to stimulate autophagy, to remove protein aggregates [2] including alpha-synuclein [3], and to slow neurodegeneration and clinical progression in several animal models [4].

Several trials have been performed with lithium in neurodegenerative diseases, including amyotrophic lateral sclerosis and mild cognitive impairment [5–9]. Other trials are currently ongoing in Alzheimer's disease, spinocerebellar ataxias, progressive supranuclear palsy, corticobasal degeneration, stroke, and primary progressive multiple sclerosis (www.clinicaltrials.gov).

Considering the previous points, we decided to test the safety and tolerability of lithium in MSA in a 48-week, randomized, placebo-controlled, pilot trial.

Methods

The primary endpoint of the study was the number and frequency of serious and non-serious adverse events (AEs). Secondary endpoints were disease progression and quality of life, and were assessed by a blinded rater. Disease progression was assessed with the Unified Multiple System Atrophy Rating Scale (UMSARS) [10], and with magnetic resonance spectroscopy. Quality of life was assessed using the EQ-5D, and depression with the Beck's Depression Inventory (BDI-II) [11]. Inclusion criteria were: clinical diagnosis of probable MSA [12], age >18 years. Exclusion criteria were: cardiomyopathy, nephropathy, hepatopathy, thyroid dysfunction, sick sinus syndrome, hyposodemia, pregnancy and/or breastfeeding, treatment with diuretics, ACE inhibitors, NSAIDs, corticosteroids, aminophylline, and mannitol.

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The Ethics Committee approved the clinical trial, and it was registered at www.clinicaltrials.gov (NCT00997672). Patients were enrolled at the Department of Neurological Sciences of the Federico II University of Naples, Italy. A Data Monitoring Committee (DMC) analysis was planned 1 year after the first randomized patient.

Lithium was administered starting from 150 mg twice-daily. The dose was increased until serum lithium levels reached 0.9–1.2 mmol/L. The maximum allowed dose was 1,500 mg/day. Randomization was performed at our study center using kit number as a randomization number, with a first-in first-out method. An independent pharmacist, using a table of random numbers, assembled the randomization list in blocks of two.

Twenty patients were planned for the trial. Samples size was not calculated, as the trial was intended as an exploratory study. Statistical analysis of number and duration of adverse events, baseline UMSARS, BDI-II, EQ-5D, age and age at onset, disease duration was conducted with the Mann–Whitney test. Fisher's exact test was used to compare gender distribution between groups. Survival analysis was performed with the logrank (Mantel–Cox) test in order to evaluate the rate of abandon/death in lithium and placebo groups. We considered P values less than 0.05 to be statistically significant. Analysis was performed using SPSS software version 18.0.3 for Mac OSX (IBM, Chicago, USA).

Results

Ten patients were enrolled, nine were randomized, four received lithium, and five received placebo (Fig. 1). None of the baseline variables was significantly different across treatment (Table 1). All patients presented at onset with a predominance of cerebellar ataxia (MSAc). They developed parkinsonian features during disease progression. Duration of experimental treatment, serum lithium at last visit, and reason for exclusion are shown in Table 1.

One year after the first patient was randomized, an interim analysis was performed by an independent DMC, with the final decision to stop the trial. Death and trial abandon were considered the same event in the survival analysis that showed a proportion of trial abandon/death of 100 % (4/4) in the lithium and 20 % (1/5) in the placebo group ($P < 0.01$). After correction for treatment duration, the number of AEs was higher in the lithium group (58.4 vs. 21; $P < 0.02$). Mean duration of AEs was higher in the lithium group, but it did not reach significance (59 ± 43 vs. 36 ± 41 days; $P = 0.072$).

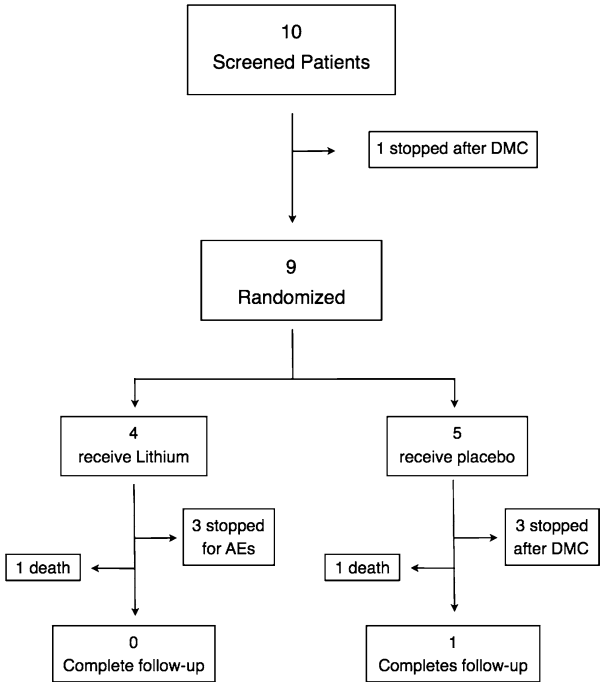

Fig. 1 Study flow-chart

Discussion

The trial was stopped because the number of AEs (primary endpoint) was higher in the lithium group. This reached statistical significance 1 year after the first patient was randomized to treatment (class II evidence). At that point half of the planned patients had been enrolled. High drop-out and elevated death rates are constant findings in clinical trials in MSA [13, 14]. Nevertheless, AEs to lithium forced all of the treated patients to abandon the trial prematurely.

Of the AEs leading to discontinuation, daytime sleepiness and tremor were related to the study drug by the investigator. Both are known side effect of lithium. The remaining AEs were considered as not related, but still forced patients to discontinue the trial.

No conclusions can be drawn on the effects of lithium on secondary endpoints of the study, since no treated patient reached the 24-week checkpoint when clinical re-assessment was planned.

Limitation of the study is small sample size of nine randomized patients. This may have determined uneven distribution of AEs due to random variation. Taking into account these limitations, we do not encourage future studies with lithium in MSA patients. Alternative treatments should be used if comorbidity of psychiatric disorders occurs in MSA.

Table 1 Demographics, baseline endpoints, and study termination for all randomized patients

Patient	Age	Sex	Age at onset	Disease duration (months)	Onset form	Group	UMSARS	EQ-5DVAS	BDI-II	MRS CBL	MRS BG	Treatment duration (days)	Serum lithium (MEq/L)	Reason for exclusion
1	60	M	58	26	MSAc	P	39	50	18	1.27	2.06	223	0.0	Death (cardiovascular failure, pulmonary infection)
2	64	M	54	119	MSAc	L	54	30	34	0.98	2.45	137	1.0	Death (cardiovascular failure)
3	70	M	68	23	MSAc	L	48	50	6	0.91	1.82	45	0.8	Fever, lower limbs weakness
4	63	M	51	143	MSAc	P	66	25	6	0.88	3.05	C	0.0	–
5	62	M	54	95	MSAc	P	67	50	39	1.18	1.61	C	0.0	–
6	68	F	65	33	MSAc	L	67	40	18	1.07	3.14	96	0.9	Daytime sleepiness, tremor, inguinal abscess
7	59	F	54	59	MSAc	L	52	50	19	–	–	76	0.5	Lower limbs weakness
8	58	M	52	58	MSAc	P	56	30	11	0.86	1.81	C	0.0	–
9	75	M	64	75	MSAc	P	45	50	16	0.78	1.97	C	0.0	–
All patients	*64 ± 5*	–	*58 ± 6*	*78 ± 46*	–	–	*55 ± 10*	*42 ± 11*	*19 ± 11*	*0.99 ± 0.17*	*2.24 ± 0.58*			
Lithum	*65 ± 5*	–	*60 ± 7*	*59 ± 43*	–	–	*55 ± 8*	*43 ± 10*	*19 ± 11*	*0.99 ± 0.08*	*2.47 ± 0.66*			
Placebo	*64 ± 6*	–	*56 ± 5*	*94 ± 46*	–	–	*55 ± 12*	*41 ± 12*	*18 ± 13*	*0.99 ± 0.22*	*2.10 ± 0.56*			

Italicized values are shown as mean ± SD for all patients, and for the lithium and placebo groups

L lithium, *P* placebo, *MSAc* MSA of cerebellar onset, *UMSARS* unified multiple system atrophy rating scale, *BDI-II* Beck's depression inventory, *EQ-5DVAS* visual analog scale of the EQ-5D, *MRS CBL* magnetic resonance spectroscopy of the cerebellum, *MRS BG* magnetic resonance spectroscopy of the basal ganglia; for both the *N*-acetyl-aspartate/(choline + creatine) ratio is shown, *C* completed the whole trial

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Conflicts of interest The authors report no competing interests.

Ethical standard All human studies must state that they have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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