LETTER

Reply to Bedlack *et al.*: A small pilot study calls for large clinical trials to evaluate the effects of lithium before prescribing the drug for amyotrophic lateral sclerosis

In response to the letter from Bedlack *et al.* (1), our small clinical study (2) represents a preliminary screening for potential neuroprotective effects of lithium in ALS, in line with the need for small studies to select new drugs to be tested in large clinical trials (3). This pilot study was based at Istituto Neurologico Mediterraneo, Istituto Di Ricovero e Cura a Carattere Scientifico (IRCCS) Neuromed in Pozzilli (IS), Italy (protocol deposited on June 14, 2005; registered by the Trials Office on June 21, 2005; approved by the Ethical Committee on July 26, 2005). At the time of publication, we were not aware of the potential to register such studies internationally, a procedure we fully endorse and are using for the multicenter follow-up.

Forty-four patients were selected from a total of 70 patients who, at the time of the study, were referred to us. The inclusion was based on the following criteria: male or female aged >30 years with definite or probable sporadic ALS (El Escorial revised criteria); disease duration <5 years; on therapy with riluzole >6 months; forced vital capacity (FVC) >70% of predicted value; ALS functional rating scale-revised (ALSFRS-R) score >20 and Medical Research Council (MRC) score never <4 in each muscle groups (neck flexors/extensors, shoulder adductors/abductors, forearm flexors/extensors, wrist flexors/extensors, first dorsal interosseus, hip flexors/extensors and adductors/abductors, thigh flexors/extensors, foot flexors/extensors). Exclusion criteria were as follows: cardiological diseases, renal or hepatic failure, hypothyroidism, severe endocrine or hematologic diseases, history of intolerance to lithium, concomitant therapies not compatible with lithium and diagnosis of motor neuron diseases other than ALS, the presence of life-supporting therapies. Multifocal motor conduction blocks were excluded both in the ulnar (axilla, elbow, and wrist) and deep peroneal nerve (caput fibulae and ankle). Abnormal blood levels of antibodies against *Borrelia burgdorferi*, gangliosides GM1, GM2, GD1a, GD1b, sulphatides, myelin associated glycoprotein, glutamate decarboxylase, kappa and lamba antibody light chains (also in urine), monoclonal immunoglobulins, neurooncogene and paraneoplastic antigens were also excluded. We randomly assigned patients to lithium treatment by using a 16-number sequence generated by a computer. Thus, groups were as follows: 16 patients receiving riluzole + lithium and 28 patients receiving riluzole only. No placebo was administered. This was an "active comparator" study aimed, for ethical reasons, to compare the test treatment (lithium) to the standard-of-care therapy (riluzole). Moreover, we recruited fewer patients for lithium because it was the first time of testing lithium in ALS ("not balanced design"). Patients were not blind to treatment and neither was the on-site neurologist, who adjusted the oral dose of lithium to plasma levels and monitored side effects and adverse events. However, the clinical evaluator for neurological scales did not work routinely on-site and was not allowed to exchange any information either with patients or with the on-site neurologists ["single blind evaluator," where the blinding refers to the examining physician, (4)]. The oral dose and mostly the plasma concentration (0.4–0.8 mEq/liter, with >80% ranging from 0.4–0.6 mEq/liter) of lithium was selected to inhibit phosphatidylinositol turnover on the basis of preclinical data to activate autophagy and to minimize the chance of side effects. We had neither dropouts nor noticeable side effects. Potential occurrence of adverse events was recorded throughout the study by the on-site physician referring to a routine table (time, severity, drug-related, duration, related safety procedures).

Use of BiPAP, mechanical ventilation and PEG never occurred in the lithium group. In contrast, all patients who died ($n = 8$) in the riluzole-only group had used these life-supporting treatments.

These results are preliminary findings to plan safety and efficacy of large clinical trials. The results of this pilot study should not represent in any way a reason to start prescribing lithium off-label for ALS.

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2. Fornai F, *et al.* (2008) Lithium delays progression of amyotrophic lateral sclerosis. *Proc Natl Acad Sci USA* 105:2052–2057
3. Gordon P, *et al.* (2007) Outcome measures for early phase clinical trials. *Amyotroph Lateral Scler* 8:270–273.
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