

Interruption of Italian lithium carbonate trial in ALS due to lack of efficacy and serious concerns about toxicity

On February 2008, a paper by Fornai and collaborators has been published on the journal PNAS about the use of lithium carbonate in a small series of 16 patients with amyotrophic lateral sclerosis (ALS). According to that study, lithium carbonate showed positive effects on disease progression and patients' survival, with few or no adverse events. On the basis of these extremely promising results in a disorder with a severe progressive and disabling course, a double blind, randomized, parallel group, dose-finding trial started on May 2008. The study involved 20 Italian ALS centres and was planned to last 15 months.

Patients were randomized to two target serum levels of lithium, one identical to the target dose of Fornai's paper (0.4-0.8 mEq/L) and the second lower (0.2-0.4 mEq/L). The lower dose is usually considered subtherapeutical and has been chosen as a pseudo-placebo. Patients were also receiving riluzole.

A total of 171 patients have been recruited. The interim analysis, performed in October 2009, has found that 60% of patients did not complete the trial (37 due to death/tracheostomy; 35 for severe adverse events; 29 for discontinuation due to lack of efficacy and 2 for lack of compliance). The very high level of trial discontinuation (about 2.5 times higher than that observed in any other trial on ALS), and the elevated toxicity of the drug in particular in ALS patients with respiratory disturbances (FVC<80%) prompted the steering committee to stop immediately the trial.

Data analysis collected at the time of study interruption has clearly shown that the two doses of lithium carbonate used in the trial did not differ significantly in term of patients' survival, disease progression and frequency and type of severe adverse events. Furthermore, using as a benchmark data of the Piemonte and Valle d'Aosta Register for ALS, an Italian prospective epidemiological register, survival of patients receiving the two doses of lithium carbonate was identical to what observed in patients of the Italian register randomly paired by age at onset and gender, indicating that lithium carbonate in this trial had no positive effect on patients' survival.