

The Lithium clinical trial

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In a recent phase II clinical trial in Machado-Joseph disease/Spinocerebellar ataxia type 3 (MJD/SCA3), a disorder without specific therapy, no significance on primary efficacy outcome – NESSCA score - was obtained. However, after 48 weeks of double-blind observation, possible benefit of lithium carbonate therapy appeared on secondary outcomes related to ataxia – SCAFI and CCFS. These apparently conflicting results may suggest that the study protocol should be revisited before ongoing on further studies. Therefore, unplanned subgroup analysis of this data was performed, as hypothesis generating technique for future studies. Treatment response modifiers and metric properties of clinical

scales were also done. Sixty-two MJD/SCA3 patients had been randomly assigned (1:1) for the 48 weeks, single center (Hospital de Clínicas de Porto Alegre, Brazil), double-blind, placebo-controlled trial. We performed additional analysis with the subscores of the Neurological Examination Score for the Assessment of Spinocerebellar Ataxia (NESSCA) and the Scale for the Assessment and Rating of Ataxia (SARA) and with the subgroup of patients with independent gait. Potential interactions of clinical/molecular findings with treatment response; minimally important differences (MID); and sample size estimations (with placebo data) of NESSCA, SARA, Spinocerebellar Ataxia Functional-Index (SCAFI) and Composite-Cerebellar Functional-Score (CCFS) were evaluated. Interventions were Lithium carbonate (target serum level of 0.5-0.8 milliequivalents per liter) or placebo tablets. Cerebellar NESSCA (range: 0-7 points) differed between groups 0.64 points (95% CI 0.23 to 1.05, $p < 0.001$) over the whole 48 weeks of study, favoring lithium. NESSCA ($p = 0.010$) and SCAFI ($p = 0.015$) differed between groups in the subgroup of patients able to perform the 8-meters walking-time, favoring lithium. Estimated sample sizes with the evaluated scales were provided for future trials with lithium or other candidate drugs. Lithium efficacy on cerebellar NESSCA and on SCAFI and CCFS in the primary analysis suggests lithium efficacy on cerebellar features of MJD/SCA3. The interaction of disease severity with treatment response on SCAFI and NESSCA indicates that early stages patients should be preferentially recruited in future studies. We suggest that SCAFI should be utilized as the primary outcomes for phase 2 studies. SARA data from this phase 2 study with positive results on SCAF should provide sample size estimations for phase 3 trials with the same intervention, where SARA should be the primary outcome. The

inclusion of independent walking patients only (according to 8MW) is advisable.

And finally, taking SARA MID and SARA progression in the placebo group as references, we suggest that future phase 3 studies should be planned for lasting at least 18 or 24 months.