When a negative trial in ALS has a positive effect on research

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In the past 5 years, amazing progress has been made in the development of therapies for amyotrophic lateral sclerosis (ALS). New genetic causes have been identified, including the *C9orf72* hexanucleotide repeat, *TDP43*, *TBK1*, and others,[1] which have provided key insights into underlying mechanisms and catalysed the development of new models for drug discovery. Additionally, in 2017, the US Food and Drug Administration approved edaravone for the treatment of patients with amyotrophic lateral sclerosis,[2] and the pipeline of amyotrophic lateral sclerosis therapies in clinical development continues to grow.

In *The Lancet Neurology*, Albert Ludolph and colleagues[3] report a double-blind, placebo-controlled, multicentre clinical trial of rasagiline (1 mg/day) as an adjunct treatment to riluzole in 252 participants with amyotrophic lateral sclerosis. No difference between the rasagiline and placebo groups was reported for the primary outcome of survival, or for any of prespecified secondary outcomes of functional decline (measured by change of total score of Amyotrophic Lateral Sclerosis Functional Rating Scale Revised [ALSFRS-R]), change of slow vital capacity, and change in individual quality of life according to the Schedule for Evaluation of Individual Quality of Life (SEIQoL).

Post-hoc analysis stratifying the trial participants into two groups on the basis of median ALSFRS-R progression rate at baseline suggested that rasagiline might modify disease progression in a subset of patients. Participants with an ALSFRS-R rate of decline greater than 0·5 points per month had improved survival at 6 and 12 months, and slower functional decline occurred in the rasagiline group compared with placebo. Participants with an ALSFRS-R rate of decline of 0·5 points per month or less at baseline appeared to decline slightly faster in the rasagiline group compared with placebo. There was no benefit of rasagiline on quality of life or breathing capacity in any post-hoc analysis groups.

Ludolph and colleagues[3] correctly describe their post-hoc analyses as preliminary results that require confirmation in a clinical trial that excludes patients with slow-progressing disease. This proposed patient selection highlights the importance of cohort enrichment to overcome the challenge of disease heterogeneity in clinical trials of people with amyotrophic lateral sclerosis. This heterogeneity could have biological or clinical sources, or both. One of the challenges for drug development in amyotrophic lateral sclerosis is that the clinical manifestations could represent a group of diseases with heterogeneous biological causes. This hypothesis is supported by the discovery of several genes that affect different molecular pathways, but lead to a similar phenotype that clinically manifests as amyotrophic lateral sclerosis. If this hypothesis is correct, cohort enrichment strategies should be focused on biological selection criteria for trial participants (eg, causative mutations), as is being done in an ongoing gene therapy trial (NCT02623699). The other challenge for such trials is the high clinical heterogeneity in the disease progression rates, which reduces the statistical power and increases the needed sample sizes for phase 2 and 3 clinical trials. Ludolph and colleagues'[3] proposed cohort enrichment strategy aims to exclude outliers with slow-progressing disease to decrease the clinical heterogeneity in the future trial population, and increase the statistical power to test the benefit of rasagiline treatment on survival. A similar cohort enrichment strategy has proven to be successful in the trial of edaravone.[2]

The results of post-hoc analyses are hypothesis generating, rather than confirmatory, and can help to maximise the findings from a clinical trial, identify potential responsive subpopulations, and pave the way for improved trial designs. At the same time, post-hoc analyses should be interpreted with caution because these results might not be reproducible. In the past 10 years, the hopes of the amyotrophic lateral sclerosis community have been raised by the results of preliminary trials that were positive, but could not be confirmed in larger follow-up trials. In a double-blind, placebo-controlled trial in 102 patients with amyotrophic lateral sclerosis, dexpramipexole showed slowing of the rate of functional decline and improved survival;[4] however, the treatment was ineffective when tested in a phase 3 trial of 942 patients.[5] Another example of false-positive results is the initial phase 2 trial of NP001 in 136 patients, in which the primary analyses were negative but the post-hoc subgroup responder analyses identified more trial participants who had no disease progression in the NP001 groups

compared with placebo.[6] The follow-up phase 2 trial failed to replicate the post-hoc results of the previous study, and missed all primary and secondary endpoints (NCT02794857). Factors such as inadequate statistical power, regression to the mean, or reliance on post-hoc results might explain why the initially positive results could not be reproduced.

Ludolph and colleagues[3] report a well conducted placebo-controlled clinical trial of rasagiline that was negative for all of the prespecified primary and secondary outcomes. However, the post-hoc analyses provide valuable data that can be used for planning cohort enrichment strategies in future clinical trials of patients with amyotrophic lateral sclerosis.

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I declare no competing interests.

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