The Challenge of Recruiting Newly Diagnosed Riluzole-Naïve ALS subjects to Clinical Trials: The MIROCALS Experience

PN Leigh on behalf of the MIROCALS Consortium*

BACKGROUND: MIROCALS (Modifying Immune Responses and Outcomes in ALS) is a randomised placebo-controlled phase-II trial assessing the safety and efficacy of low dose interleukin-2 (ldIL-2) as an add-on therapy to riluzole, in incident riluzole-naïve ALS patients.

Following a 3 month 'run-in' to insure tolerance to riluzole, subjects are randomised (1:1) to ldIL-2 or placebo and followed up for 18 months. The primary efficacy outcome is survival.

Main inclusion criteria included El Escorial criteria (possible to definite), Age (18-75), SVC (≥ 70%), disease duration (≤24 months), and successful LPs at inclusion and randomisation. Main exclusion criteria linked to the therapy included active infection, immunomodulating treatments (eg chronic steroids, DMARDs), immuno-suppressors, and history of AIDs and/or cancer.

The study incorporates extensive biomarker investigations on blood and CSF (from baseline to 4 months post-randomisation) with primary focus on assessing drug target engagement, and disease activity response to treatment.

The recruitment target is 216 randomised subjects to demonstrate with 80% power a twofold decrease in risk of death at 18month.

OBJECTIVE: To make a preliminary analysis of the characteristics of the MIROCALS 'de novo' ALS population recruited into the study between June 2017 and October 2018 in relation to key prognostic factors.

RESULTS: As of 25th October 2018 the study is still recruiting in 17 ALS Centres (7 UK, 10 FR), and 184 subjects have been enrolled. Site of onset ratio (bulbar versus limb) was 0.32; female to male ratio was 0.59; mean ± sd age at disease onset was 57 ± 11 years; durati on of symptoms prior to entry was 11 ± 5 months. ALSRS-R total score at recruitment was 41 ± 5 and rate of progression since onset was 0.8 ± 0.7 points/month. SVC was 93 ± 18 % predicted. Overall, 32% of the 144 enrolled subjects who completed run-in could not be randomised due to disease progression (12%), riluzole intolerance (4%), or failure at screening (16%).

CONCLUSIONS: Athough the de novo ALS population represents about 10% of the overall population of this rare disease, the MIROCALS collaboration has shown that it is feasible to recruit newly diagnosed ALS subjects who have not been started on riluzole into a large Randomised Controlled Trial. Furthermore, repeat LP was acceptable, and not a common reason for drop out either at inclusion or randomisation. However, there was a higher than expected rate of failure to randomisation resulting in the need to increase the number of subjects recruited.

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