Slow Progressors in Edaravone Trial: Is the Edaravone study a statistical artefact?

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Abstract

Over the past two decades the El Escorial (EE) criteria have been used for trial inclusion in the major randomized control trial (RCT). One of the goals of the revised EE criteria was to allow earlier diagnosis and thus earlier trial inclusion by introducing a new category namely "clinically probable-laboratory supported ALS". This category allowed EMG findings to be taken into account assuming that EMG is more sensitive that the clinical examination in detecting lower motor neuron signs. Recently, Edaravone has been licensed in several countries for the treatment of ALS based on a rather small RCT in a selected group of ALS patients excluding the EE "clinically probable –laboratory supported ALS" category. The major reason was that in a post hoc analysis of the first Edaravone trial this group compromised many slow progressors. As it is unclear whether this bias towards slow progressors was a study specific problem (as it was only conducted in Japanese patients) or related to the category itself, we performed an analysis in the PRO-ACT database asking the following questions: 1. Was it correct to exclude the probable –laboratory supported ALS" category from the trial ? 2. Is the bias towards slow progressors in the "probable-laboratory supported ALS" also present in a large scale database?

In the PRO ACT database, including 1282 ALS patients, progression in the "probable-laboratory supported ALS" category was significantly slower (- 0.53 in ALSFRS/month) compared to the other EE categories (-0.68 in ALSFRS/month; $p<.001$). Furthermore, the "probable-laboratory supported ALS" category exhibited a significantly longer diagnostic delay (13.5 months) as compared to the other EE categories (11.7 months, $p<0.012$). This suggests that there is not only a bias towards slow progressors in the "probable-laboratory supported ALS" category, but also that the "probable – laboratory supported ALS "category does not fulfil the previous goal of earlier diagnosis. Thus, the exclusion of the "probable-laboratory supported ALS" category from the Edaravone trial was justified.