Novel concept to evaluate efficacy of therapeutics for ALS based on patient preference

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A novel composite scale (PROOF, incorporates patient's perception of disease burden to motor functional evaluation for ALS.

Efficacy of therapeutics for neuromuscular diseases has been assessed using critical events such as survival or quantitative or semiquantitative functional scales. Most of such scales consists of items which can be clustered into several functional domains, and total scores are widely used as indices of overall function. For amyotrophic lateral sclerosis (ALS), the revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) which contains 12 items belonging to four functional domains, bulbar, fine motor, gross motor and respiratory, has been widely used in clinical trials as a co-primary endpoint with survival, but it does not reflect the variability in patients' perception of disease burden. The paper by van Eijk *et al* reports a new concept to evaluate the therapeutic efficacies in ALS clinical trials by considering patient preference for assessing ALSFRS-R: Patient-Ranked Order of Function (PROOF).[1]

PROOF is a composite endpoint of the ALS clinical trial that ranks objective measurements from the ALSFRS-R, according to the patient's perspective, rather than simply using the total score. By weighting the objective ratings in the order of importance to the patient, PROOF enables to balance objective functional analysis with the patient's perception of importance. Throughout this paper, the authors tell us that researchers should have their interests not only in improving the total ALSFRS-R Score because the patients might consider the drug's domain-specific improvements in the ALSFRS-R to be less important, and furthermore, obsession with the total score alone might reduce the statistical power of the clinical trials.[1]

Quality of life (QoL) and other patient-reported outcome measures (PROMs) have increased their presence not only in patient-centred care but also in therapy development. Recently, the Federal Drug Administration and European Medicines Agency issued guidelines to support the use of PROMs in clinical trials for new drug development.[2 3] For developing PROMs, weighting items or domains is a key element for patient preference-based assessment.[1] An attempt to adopt each individual's perspective in QoL evaluation has been made for various diseases including neurological disorders. For instance, the Schedule for the Evaluation of Individual QoL-Direct Weighting is often used for evaluating QoL of patients with multiple sclerosis.[4] However, individualisation of motor functional assessment has not been developed. PROOF is an ingenious approach to take patients' preference into account for functional evaluation which has been solely dependent on rater's assessment.

There are still some issues to be solved for using PROOF in clinical studies. What this method provides is a relatively abstract measure of winning probability, the effect size cannot be calculated as a score. Introducing minimal clinically important difference with a certain threshold may help to interpret the winning probability. Cognitive impairment is another obstacle for PROOF, because certain population of patients with ALS has cognitive decline. Application of PROOF in future clinical trials will lead to validation of this measurement.

With a rapid growth of translational science, patient-centred assessment in clinical trials is now becoming active in various fields of neurology. Similar strategies as PROOF should be applied to other neurological disorders.

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