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Commentary

Can I Be Honest With My Neurologist? A Problem of Health Technology Assessment in Canada

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Clinical trials of new drugs for amyotrophic lateral sclerosis (ALS) typically attempt to include patients who are considered the most likely to allow detection of an efficacy signal based on diagnostic criteria, disease duration, and functional status. Many patients are thereby precluded from participating in such trials because of the wide range of ALS phenotypes. Importantly, these criteria have also become the basis for decisions by Health Technology Assessment (HTA) agencies to restrict patients' eligibility for reimbursement of drug costs under private and publicly funded insurance plans, to only those who strictly conform to clinical trial inclusion criteria. The basis for such criteria as evident in current literature and their impact on patients' access to treatment are discussed in this commentary from the perspective of a person living with ALS (pALS).

Survey of ALS Clinical Trial Criteria

Inclusion and exclusion criteria for 58 of 125 sequential entries of interventional trials in the National Library of Medicine database (ClinicalTrials.gov) were reviewed in August 2023 for "drug trials Phase 2 or 3" in non-familial amyotrophic lateral sclerosis. There were 5 Phase 1 or "1,2" trials (9%), 38 Phase 2 (65%), 14 Phase "2,3" (24%), and 1 Phase 3 (2%) trials. An El Escorial (EE or rEE) or Awaji diagnosis was required by 42 trials (72%) of which 14 restricted inclusion to "Definite" or "Probable" ALS, while only one trial used Gold Coast criteria. An upper limit on symptom duration was imposed by 43 trials (74%) (range 18–60 months: 8 (14%) 18 months and 11 (19%) 24 months). Limits on ALS Functional Rating Scale-Revised (ALSFRS-R) scores, regarding disease progression rate, total score, or individual functional item scores were imposed by 15 trials (26%).

Diagnostic Criteria

Formal diagnostic criteria for ALS were developed by the World Federation of Neurology almost 30 years ago (the EE criteria). Revisions were made in 1999 (the Airlie House Criteria – rEE) and again in 2007 (the Awaji criteria). These criteria established a hierarchy of definitions for the probability of an ALS diagnosis based on the number of body areas affected with upper motor neuron (UMN) and lower motor neuron signs and symptoms.

However, a substantial consensus now holds that EE criteria can be a barrier to appropriate diagnosis because of their poor inter-rater reliability, an incorrect implication of varying levels of diagnostic uncertainty, and their inadequate sensitivity for making the diagnosis across ALS phenotypes. Only a minority of patients meet EE criteria for "Definite" ALS at the time of their clinically confirmed diagnosis, and some may not even meet it at the time of death due to ALS. Even patients with an initial diagnosis of the lowest EE category ("Possible" ALS) may die of ALS while still categorized as "Possible." Since a significant proportion of patients who meet the 2019 Gold Coast criteria for a confirmed diagnosis of ALS do not meet the EE definitions of "Possible" or "Probable" ALS, their replacement by the Gold Coast criteria has been proposed because they have greater sensitivity than the EE criteria with a similar level of specificity.

Clinical Trial Criteria

Clinical trials of new drugs for ALS invariably include assessment of patients' functional ability and/or mortality. Ensuring that the trial can provide statistically valid conclusions as expeditiously and efficiently as possible requires inclusion of patients who have both adequate functional ability and can also be expected to reach the trial end points over a manageable time frame, such as 6 months. These are patients representing the "classical" presentation of ALS rather than the subtypes with slower disease progression, and their selection for clinical trials is facilitated by the use of the restrictive probability definitions within the EE framework, as well as limits based on ALSFRS-R scores, and time since the first onset of symptoms. In fact, the majority of trials surveyed required patients to meet EE diagnostic criteria, one-third restricted inclusion to patients with definite or probable ALS, and one-third required a disease duration of 18 or 24 months, or less.

However, the functional ability and life expectancy of patients with ALS vary greatly. While the median duration from ALS onset to death is approximately 2–3 years, approximately 50% of patients live 3 or more years after diagnosis, about 25% live 5 years or more, and 10% live more than 10 years. Not only does the inherent rate of disease progression vary considerably between patients, but the time of diagnosis also depends on factors such as patients' own level of awareness of upper and lower motor neuron symptoms,

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willingness to seek medical follow-up, and variable access to physicians with the expertise to evaluate possible symptoms of ALS and make a neurophysiologically confirmed diagnosis. In Canada, the time interval between patients' awareness of signs that can be associated with the onset of ALS and a conclusive diagnosis by a specialist can be 2 years or more, thus eliminating those patients from clinical trial participation.

Reimbursement Criteria

While population enrichment through the use of restrictive clinical trial inclusion criteria is a valid approach to trial design, inequity of drug access can result when they are also used to determine patients' eligibility for drug cost reimbursement. The lack of sensitivity of the EE criteria for the diagnosis of ALS should preclude their use in formulating reimbursement criteria for new drugs for ALS. Criteria based on disease duration are also inappropriate as the basis of reimbursement decisions, since they are dependent on a standardized and precise determination of time of symptom onset among a wide range of possible definitions and they lead to inequity because they do not account for interpatient variability in diagnostic delay. As a dramatic example of this, the combination of a maximum disease duration of 18 months with a definite EE diagnosis was shown to potentially eliminate over 90% of ALS patients from eligibility for the coverage of the costs of Albrioza (Relyvrio) under provincial drug plans that use the criteria imposed by the Canadian Agency for Drugs and Technologies in Health (CADTH).[1]

Restrictions on scores on the ALSFRS-R for clinical trial inclusion also have implications for current approaches to HTA. The pivotal clinical trial that led to regulatory approval of the intravenous and oral formulations of edaravone (Radicava) in Canada and the US required that patients not only have a diagnosis of "Definite" or "Probable" ALS within the past 2 years and adequate respiratory function but also a defined level of function for performing activities of daily living – specifically, a score of at least 2 on all items of the ALSFRS-R. While this may be both desirable and valid as a population enrichment strategy for clinical trials, the use of single item scores on the ALSFRS-R overlooks the deficiencies in the biometric properties of this scale. It is recognized that a one-point change on a particular item can represent differing amounts of functional change depending on the item, and for some items, a one-point changes on the scale can represent a change in a domain other than function. The ALSFRS-R may also lack responsiveness to detect change when change has actually occurred, as shown by the examination of pooled clinical trial databases where significant proportions of placebo-treated patients show no change in ALSFRS-R scores over 6 months or even 1 year.

It is therefore impossible to ascertain the significance of a reduction in score from 2 to 1 on a single item of the ALSFRS-R for a patient's overall functional state, or capacity for response to an effective treatment. Nevertheless, the criteria issued by the CADTH would preclude provincial drug plan coverage of Radicava for patients who have functional impairment in a single domain and score less than 2 on a single item on the ALSFRS-R (e.g. climbing stairs with assistance from a handrail, or having help with cutting food) but are otherwise adequately functional.

Given the finite budgets of the provincial drug benefit plans, it is understandable that CADTH would seek to restrict access to drugs for rare diseases such as ALS. These drugs have high cost in relation to their effectiveness, when estimated in terms of length of life remaining and its associated quality, and expressed as cost per quality-adjusted life year (QALY). The use of restrictive clinical trial inclusion criteria to determine eligibility for coverage under provincial drug benefit plans therefore provides a practical approach to cost containment for such drugs.

However, these restrictions on drug access presume that the mechanisms of motor neuron death differ between the ALS subtypes with classical versus slow progression and that the response of those mechanisms to drugs that slow motor neuron death differs between these subtypes. There is now significant evidence from studies examining structural and functional changes in the brains of ALS patients that such changes are common to all forms of ALS, including the almost universal finding of aggregations of the TDP-43 protein in the brain. The Canadian ALS Neuroimaging Consortium (CALSNIC) has demonstrated that levels of N-acetylaspartate (NAA), a marker of neuron loss or dysfunction in the cerebral motor cortex, were reduced in patients with ALS, relative to healthy controls. Importantly, NAA was significantly reduced in patients with both fast and slowly progressing disease as well as in those with a lower or higher burden of UMN involvement, while reductions in NAA were greater in those with faster progressing disease and greater UMN involvement.[2] It is hoped that validation of biomarkers like NAA and neurofilaments for use as primary outcomes in clinical trials would allow inclusion of a wider range of patients and facilitate identification of drugs that slow disease progression. In turn, this should broaden the eligible population for drug cost reimbursement under provincial drug plans beyond the limits currently resulting from restrictions based on diagnostic criteria, disease duration, and functional status.

Patients with advanced disease, independent of disease duration, may well have adequate functional capacity to allow for meaningful slowing of disease progression in response to an effective treatment, as confirmed in two recent studies. A study of 3446 patients with ALS receiving riluzole compared with 1332 patients not treated with riluzole demonstrated that survival in the riluzole-treated patients was improved relative to the untreated group, independently of time elapsed from symptom onset to treatment initiation.[3] Also, re-analysis of the pivotal data from the randomized placebo-controlled trial that was the basis of the international regulatory approval of riluzole supports this conclusion. Stratification of enrolled patients, according to King's Clinical Stage, demonstrated that patients in the most advanced stage of disease (Stage 4) on riluzole had a significantly prolonged survival compared with patients treated with placebo.[4]

Conclusions

Time since symptom onset, EE diagnostic criteria and ALSFRS-R scores can be relevant to the design of efficient and expeditious trials of new ALS drugs, but they have inherent weaknesses that should preclude their use in decision-making for access to treatment of ALS. EE definitions do not have adequate sensitivity, have poor inter-rate reliability, and incorrectly communicate diagnostic uncertainty. Inter-individual variation in time since symptom onset is a reflection of the inherent heterogeneity of ALS and variability in time to access neurological evaluation, so estimates of disease duration in a given patient are imprecise. The ALSFRS-R has significant nonlinearity within its functional domains and lacks responsiveness. There is no established relationship between these clinical trial inclusion criteria and differences in underlying neuropathologic mechanisms in ALS. They do not adequately define an individual's functional state nor predict the capacity of an

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individual to respond to effective treatments that slow disease progression. There is therefore no basis for the use of these criteria in HTAs that result in restrictions on access to drug treatment for ALS. Nevertheless, the CADTH has limited reimbursement of recently marketed drugs for ALS to patients with a maximum time since symptom onset and minimum scores on single ALSFRS-R items, resulting in inequitable access to treatment.

So, can I afford to be honest with my Neurologists about symptom onset or ALSFRS-R scores – would they even want me to be? Could the consequences of clinically inappropriate reimbursement criteria be a reason for them to seek creative methods of providing patients with access to new drugs? Before Radicava was accepted for reimbursement under drug benefit plans in Canada, these methods included a lottery system for determining who received the drug from the limited supply available, differential interpretations of the manufacturer's criteria for supplying the drug, or efforts to persuade patients to wait until the drug became available under drug reimbursement programs.[5] Similar considerations may be applied to future drugs that are approved based on pivotal clinical trials that include restrictions on EE criteria, and limits on ALSFRS-R scores and time since symptom onset, when such criteria become the basis of eligibility criteria imposed by HTA agencies, thus further contributing to inequity in drug access for ALS patients.

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