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REVIEW ARTICLE

TRICALS: creating a highway toward a cure

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Abstract

A change in our current approach toward drug development is required to improve the likelihood of finding effective treatment for patients with amyotrophic lateral sclerosis (ALS). The aim of the Treatment Research Initiative to Cure ALS (TRICALS) is to extend the collective effort with industry and consolidate drug development paths. TRICALS has begun a series of meetings on how to best move the field forward collaboratively, thereby addressing five major topics in ALS clinical trials: (1) preclinical research, (2) biomarker development, (3) eligibility criteria, (4) efficacy endpoints and (5) innovative trial design. There is an appetite for ongoing discussions of these major topics in clinical trials between representatives from academia, patient advocacy groups, industry partners and funding bodies. Industry is open to fundamentally change drug development for ALS and shorten the time to effective therapy for patients by implementing promising innovations in biomarker development, trial design, and patient selection. There is however, a pressing need from all stakeholders for regulatory discussions and amendments of current guidelines to successfully adopt innovation in future clinical development lines.

Keywords: *Clinical trial design, biomarkers, preclinical, guidelines*

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Introduction

It has been nearly 25 years since the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) approved riluzole (1). Recently, edaravone was approved by the FDA for delaying motor function deterioriation (2). A benefit to life expectancy remains, however, to be determined and riluzole remains the only available treatment for European patients with amyotrophic lateral sclerosis (ALS). Over 70 compounds have been tested (3), but despite considerable efforts from industry and academia, and promising early signals, none of the treatments has been effective in slowing the course of the illness or prolonging survival. The reasons for this failure in translation from animal models to human trials are multifactorial, but can be grouped into five major categories—namely: (1) disease heterogeneity and our relatively limited knowledge of the interplay between different disease mechanisms in humans; (2) inappropriate use of pre-clinical experimental models of mechanisms and not disease; (3) an absence of biomarkers of pathogenic mechanisms, markers of disease onset, and quantitative markers of progression; (4) pharmacological challenges of dosing and measures of target engagement and (5) inefficient or poorly designed clinical trials (4–6).

There is now an urgent need to rethink the clinical development pathway for ALS treatments. This will require large-scale collaboration between various stakeholders and important adjustments to our current approaches. Hence, we established the Treatment Research Initiative to Cure ALS (TRICALS) to (1) unify academia, patient advocacy groups, industry partners and funding bodies toward a common goal in finding a cure for patients, (2) provide a harmonized, international infrastructure for the conduct of clinical trials and (3) coordinate research efforts that maximize the likelihood of successful drug development.

Currently, the TRICALS consortium consists of 40 specialized centers in 14 countries, diagnosing over 3800 patients with ALS each year. TRICALS has begun a series of meetings with industry partners to discuss how best to move the field forward collaboratively, such that the best drugs are fast-tracked to the clinic using new and appropriately designed strategies that are both scientifically robust and compliant with the requirements of regulatory authorities. Five main topics are currently being explored within this collaborative effort and are discussed below.

Preclinical and translational research

Background

Prior to clinical use, safety and target engagement of new therapeutics need to be established in experimental models. Despite its well-documented drawbacks, the superoxide dismutase 1 (*SOD1*) transgenic model remains the gold standard to obtain preclinical insights into disease-modifying properties. Although preclinical studies with *SOD1* models can in part replicate mutant *SOD1* familial ALS, the pathophysiologic processes do not seem to recapitulate the mechanisms underlying sporadic disease and animals are often treated prior to disease onset (4,7). In addition, even if a clear pathway is being examined, either in familial or sporadic ALS, there is often a lack of translational markers of target engagement. As a result, preclinical studies may falsely trigger the continuation of drugs to clinical phases.

Considerations

Optimizing preclinical study design may significantly improve the utility and predictive value of *SOD1* and other disease models for subsequent clinical trials (8). Moreover, given the rise of antisense oligonucleotide therapies (9), specific preclinical models based on a genetic mutation are likely to prove useful to evaluate preliminary drug safety profiles and pharmacodynamics (7,10). Moreover, if there is a clear pathophysiological pathway, the *SOD1* model may still serve as feasible preclinical model as long as adequate biomarkers of target engagement are being incorporated (10). It is, therefore, important to develop not only new preclinical models, but also to simultaneously advance biomarkers of target engagement. Intermediate translational steps will be required to validate and replicate these new markers of target engagement in both preclinical as clinical studies. Examples include the use of neurophysiological biomarkers in phase 1 studies (11) or misfolded *SOD1* protein levels.

Future directions

There is an acknowledged need for (1) additional models that better capture the heterogeneity of the disease and (2) markers of target engagement to improve preclinical to clinical translation. In vivo preclinical models can generate valuable insight in blood-brain-barrier permeability and, especially for small molecules, it will be critical that the relevant pharmacokinetic studies are included. Furthermore, human derived stem cell models hold promise in the determination of disease mechanisms, opening the possibility for high-throughput screening tools and personalized medicine (12).

Biomarkers

Background

Biomarkers can enhance patient selection, improve prognostication, evaluate and predict biological treatment response or serve as surrogate outcome (4,13,14). Notwithstanding, the majority of clinical trials may not optimally use biomarkers, thereby potentially missing responding subgroups, lacking the ability to quantify target engagement or subtle treatment effects, and not gain knownledge on biomarkers of the disease (4,14).

Considerations

The multicentre setting of clinical trials provide an ideal environment to evaluate the association between a biomarker and classical clinical endpoints, and to determine its reliability, test-retest validity and site variability (15). Biomarkers should be defined as to their potential utility in all phases of clinical development (e.g. markers of specific pathogenic processes; markers of specific subgroups; markers of target engagement; markers of disease progression etc) (4,5). Examples of markers that are "clinical trial ready" include neurofilaments. Neurofilaments have been shown to be stable over time and may be helpful to stratify patients and quantify treatment response (16,17). Other easily accessible biomarkers such as creatinine, inflammatory markers or urinary $P75^{ECD}$ are of potential utility and could be considered as exploratory or secondary endpoints (14,16,18).

Future directions

Neurofilaments have the potential to improve multiple aspects of ALS clinical trials and should be implemented at all stages of drug development. Other markers that could be of utility include biochemical, transcriptomic and proteomic measures, neuroimaging (including PET) and advanced neurophysiology including neuroelectric signal analysis. Combinations of different biomarkers are likely to provide additional benefit and should therefore be part of any clinical development program. Open-access initiatives and prospective data collection are vital for their validation. Ultimately, associating treatment responses on biomarkers with those on classical clinical endpoints could prove their surrogate value and thereby improve trial efficiency (19). It is thereby essential that the same biomarkers are used in all clinical trials to evaluate their surrogate value across a range of different treatment effects (20).

Eligibility criteria

Background

Eligibility criteria are the primary tool to manage population heterogeneity and increase the probability of detecting effective compounds. Classically defined eligibility criteria (e.g. fixed boundaries for symptom duration, vital capacity or diagnostic delay) are inefficient and of limited value (21,22). Inefficiencies can be attributed to the mathematical processes that are used to exclude cohorts of patients whose pattern of progression is either too fast or too slow. A univariate, step-wise application is inconsistent with the pattern of human disease, which is best defined by a multivariate combination of several characteristics (23). Using classical eligibility criteria, large numbers of patients are excluded while conferring minimal gains in population homogeneity and severely limiting the generalizability of results.

Considerations

Current eligibility criteria should, therefore, be revised. This would have the dual benefits of increasing eligibility rates and improving population homogeneity. Simple multivariate prediction rules could be defined for individual patients that optimize the use of prognostic information and improve patient selection (22). Such an approach would bypass the need for group-level univariate selection rules. Indeed, several validated prediction rules are already available for different primary outcomes (e.g. the ENCALS and Origent model for survival and functional outcomes, respectively) (23,24).

Future directions

Prediction of unfavorable disease patterns is of particular interest for industry in order to increase trial efficiency. However, prediction-based eligibility criteria are currently not part of trial guidelines and regulatory discussions are required for successful implementation in future settings.

Efficacy endpoints and follow-up duration

Background

Efficacy endpoints must be clinically meaningful, sensitive to change and reliable in test-retest settings (5,25). Composite survival endpoints and the revised ALS Functional Rating Scale (ALSFRS-R) are currently the primary measures of efficacy in ALS clinical trials (26). Nevertheless, up to now, early phase 2 trial outcomes that are based on the slope of the ALSFRS-R have translated poorly to confirmatory trials evaluating mortality (13).

Considerations

In order to improve the translational power of exploratory to confirmatory trials, the follow-up duration of exploratory trials should be increased to at least 6 months and indicate a response in biomarkers of target engagement, or in multiple clinical endpoints, prior to initiation of a confirmatory trial. As showing a therapeutic benefit on mortality is required by European regulators for market authorization (25), the follow-up duration of confirmatory trials should be increased to at least 12 months in order to design trials with feasible sample sizes (27). Halting or slowing motor neuron degeneration may be slow, and take time to manifest in trial endpoints. The power to quantify a survival benefit can be improved by employing the Joint Modeling Framework (14). In addition, remote digital technology can help to further define the real-world functional benefits of a therapeutic intervention (13,27,28), whereas extensive training on outcome measures as organized by TRICALS and Northeast ALS Consortium (NEALS) may warrant quality control and minimize endpoint variability (5,15).

Future directions

There is an urgent need to better translate exploratory clinical trials to confirmatory settings, which requires innovation of the current clinical endpoints. The ALSFRS-R has significant limitations; while it is unlikely in the short term that this scale will be replaced, the differences in slope across subscores of the ALSFRS-R should be acknowledged. Trials should be adequately powered such that the subscales of the ALSFRS-R can be analyzed individually (29). Moreover, as the ALSFRS-R does not include a cognitive domain, scales that assess cognition and behavioral aspects should also be incorporated into future trials (30), together with measures of quality of life. Clinical staging algorithms such as King's staging or MiToS staging, or neurophysiological testing, may help to identify responding subgroups and, ultimately, optimize the selection of compounds for confirmatory clinical trials (31,32). Given the differences between EMA and FDA guidelines, additional regulatory discussions may be warranted to align clinical trials across continents.

Innovative trial design

Background

The process of designing and initiating new clinical trials in ALS is a lengthy one. Currently, as new biotechnology companies enter the field, new trials are often designed from first principles rather that utilizing a previously established protocol. This leads to an unnecessary loss of resources and prior knowledge, and results in wide variability in key design characteristics such as endpoints, study duration and sample size. These arbitrary design settings are likely to miss crucial treatment clues and further delay the development of effective treatment (33). Efficient, evidence-based trial methodology that harmonizes future clinical development paths is urgently required, using agreed master protocols with design input from academic researchers, industry and patient representation.

Considerations

Multi-arm, multi-stage (MAMS) and platform designs allow investigators to evaluate multiple treatments simultaneously. These study designs act as an overarching umbrella for multiple, individual sub-studies and harmonize efficacy outcomes, visiting schemes, procedures and infrastructures. This harmonization allows for large reductions in cost, duration, sample size and eliminates the need for repeated startup delays and protocol development when new compounds are discovered (34).

Future directions

The design of a master protocol requires extensive planning, multicentre collaboration and adaptations in trial methodology. Although we recognize that elements will need to be thoroughly discussed *a priori* (e.g. sharing of placebo arms and data-sharing) (35), these initiatives can significantly improve trial efficiency and may be of particular interest for smaller biotech companies as they provide low-cost access to existing infrastructures and patient populations.

The need for regulatory reform

Industry is open to fundamentally change drug development for ALS but requires amendments of the current regulatory guidelines to successfully implement innovation in their pipeline. Major future directions and regulatory themes are:

1. Relaxing the obligation of preclinical evidence using the *SOD1* mouse model, recognizing it is a model of mechanism, not disease, and promoting alternative human-derived models
2. Requiring the use of target-engagement biomarkers to improve preclinical-to-clinical translation
3. Implementing neurofilament testing in all stages of clinical development
4. Mediating the use of ALSFRS-R subscales, cognition, staging, advanced electrophysiology and digital health technology to enhance the detection of early efficacy
5. Training on outcome measures to ensure high quality data and minimize endpoint variability

6. Optimizing the adoption and implementation of prediction models in the design and analysis of clinical trials
7. Promoting the use of harmonized, innovative and adaptive clinical trial design to maximize efficiency
8. Advocating the adoption of unified electronic patient records and digital biomarker collection

Conclusion

There is an appetite for ongoing discussions of major topics in clinical trials between representatives from academia, patient advocacy groups, industry partners and fundraisers to consolidate our current approach toward drug development for ALS. Addressing these key topics will require further dynamic discussions with all stakeholders, and the EMA and FDA. Ultimately, real-world implementation in a large-scale collaboration such as TRICALS could significantly accelerate innovation in drug development for ALS and create a highway toward a cure.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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