Opportunities for improving therapy development in ALS

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Abstract
In May 2013, The ALS Association and The Northeast ALS Consortium (NEALS) convened a meeting of stakeholders for a round-table discussion of ways to improve therapy development in ALS. The following overview summarizes issues raised and potential new directions discussed at the meeting. We recommend that future phase II clinical trials in ALS proceed when the proposed treatment is directed at targets that are likely to be involved in ALS pathogenesis in a defined subgroup of patients, and be accompanied by one or more biomarkers to track both clinical progression and pharmacodynamic engagement of the target. Innovations in trial structure and design, and greater involvement of patient advocates, may also improve trials.

Key words: Amyotrophic lateral sclerosis, clinical trials, biomarkers, therapy

Introduction
In May 2013, The ALS Association and The Northeast ALS Consortium (NEALS) convened a meeting of clinical researchers, regulatory authorities, industry representatives and patient advocates for a round-table discussion of ways to improve therapy development in ALS. The following overview summarizes issues raised and potential new directions discussed at the meeting.

Negative results from recent phase III studies in ALS have prompted the ALS research community to ask what improvements can be made in the way new therapies are brought to trial. Riluzole, the only disease-modifying therapy for ALS, was approved over 15 years ago, and has modest, early effects on ventilator-free survival and no demonstrated effect on muscle strength. One major hurdle in therapy development has been lack of understanding of disease mechanisms, which has resulted in a lack of validated targets against which to design new drugs. However, there has been substantial progress on that front with the recent discovery of several new genes, including C9orf72 and TDP-43. Not only are these genes leading to models that will provide an alternative to the SOD1 models that have dominated the field, but those models are potentially of greater pathogenic relevance, given the high proportion of familial ALS (and even some sporadic ALS) due to the C9orf72 gene, and the presence of TDP-43 inclusions in virtually all ALS patients. In addition, other models are being developed that allow for unbiased screening of pathways that influence disease progression. Finally, enhanced bioinformatics approaches may bring multiple distinct datasets (e.g., laser capture data, genetics data) to bear on identifying and prioritizing new targets in ALS. It is at least possible that we may soon be presented with new disease mechanisms, new targets, new ways to prioritize those targets, and new drugs to test against them. With that expectation, it is imperative that the trial community be prepared with the most efficient means to test new candidates, quickly identifying the most promising for larger trials while just as rapidly eliminating the rest.

Lowering the barriers to rapid and efficient phase II testing in ALS
Phase II clinical trials are the linchpin of clinical drug development, the stage at which it first becomes apparent whether a putative therapy is promising enough to proceed to a pivotal phase III trial. The goals of a phase II study are to identify a safe and tolerated dose of a candidate drug in a patient population, as well as to gain initial insights into its
potential efficacy. Ideally, a phase II trial incorporates both a test of pharmacodynamic effect, showing the ability of the drug to hit the proposed target (and the dose at which it does so most effectively), and a test of clinical relevance, testing whether engaging the target has the potential to affect some clinically meaningful outcome at safe and tolerated doses. These objectives may be incorporated into a single trial, or into multiple phase II trials. Unfortunately in ALS, the lack of well-understood pharmacodynamic targets and the lack of the tools to assess them in vivo, have meant that the primary outcome measures in many phase II trials have been strictly clinical ones; in effect, they are small phase III trials. However, the heterogeneity of ALS patients, including especially variability in rates of clinical progression, has meant that these trials are often underpowered to conclusively detect a change in clinical disease progression. In addition, heterogeneity and the inability to predict natural history progression means that hidden imbalances in small clinical trial groups may influence outcomes. As a consequence, the unbroken pattern to date has been that drugs with small positive results in phase II fail in phase III. Perhaps just as importantly, the lack of well understood targets and the lack of ability to assess target engagement have meant that results from phase II trials, whether positive or negative, have not moved the field forward in terms of understanding of disease mechanisms or target validity. Individual drugs are ruled out, but not pathways or targets.

In the face of these challenges, trial researchers in ALS have adopted several strategies to speed up phase II trials, and to make them more flexible. These have included futility analysis, interim analysis with stopping rules, and adaptive designs.

A futility analysis is designed to quickly determine if an agent has so low a chance of success that it should not be considered in a phase III trial. Futility analysis in ALS trials was introduced in a creatine trial (1). The NIH/ALSA-funded study of lithium was an efficacy study, with a preplanned interim analysis that showed there was not likely to be any benefit in continued testing, and hence was stopped (2). This was confirmed in later lithium trials that included more patients and ones with a longer disease duration (3,4). In the multi-stage trial of coenzyme Q10, the initial stage compared two doses to placebo; patients in the preferred dose group then entered the second stage, along with additional patients randomized to either active drug or placebo (5). In this trial, the futility boundary was approached but not crossed. The decision not to pursue further development was a clinical rather than statistical one.

Adaptive designs allow planned modifications based on interim data observed during an ongoing study (6). The potential for greater flexibility and efficiency makes these types of designs particularly attractive for use in disease areas such as ALS. There have been a large number of adaptations proposed in the statistical literature. However, one that appears to be very attractive to ALS researchers is an adaptive seamless design that combines what would traditionally be performed as separate studies together into a single protocol (7). As an example, the ceftriaxone trial was planned as a seamless trial incorporating phases Ib through III, first testing pharmacokinetics and then safety and tolerability in a small group of patients, with those patients then entering a 500-patient efficacy trial (8). In this study, there were no efficacy stopping rules governing the progress from phase II to phase III, as the preclinical data were judged strong enough to go forward without a phase II signal.

Further opportunities for accelerating trial development exist. In many multicenter trials, major bottlenecks occur in contract negotiation and Institutional Review Board (IRB) approval. Initial experiences with trials employing master contracts and a centralized IRB have been promising. One model for this approach has been the NeuroNEXT initiative, supported by the United States National Institutes of Neurologic Diseases and Stroke, in which the clinical coordinating center, Massachusetts General Hospital in Boston, serves as the central and only IRB of record for every NeuroNEXT protocol at all participating sites. Use of this central IRB model should reduce the time needed for approving and hence initiating the research at all sites (9). Master contracts between the NeuroNEXT Clinical Coordinating Center and each of the clinical trial sites have been established for all trials conducted within the network. Together, these practices may be able to reduce by several months or more the time-lag between study initiation and enrollment, and improve quality and consistency of multicenter trials. Other models are being tested by other consortia worldwide. It may be advantageous to establish ‘centers of excellence’ for ALS trials, sites with a highly efficient and dedicated staff that have the infrastructure (including IRB and contract agreements) in place for rapid mobilization when new agents become available. NEALS is currently piloting such a model, and first reports about the program should be available in 2014.

Improving the chances of success

While such innovations in trial design and oversight have the potential to speed up the trial process, they have not addressed the two fundamental problems hindering progress in developing and testing new treatments for ALS – patient heterogeneity and target identification and assessment.

Difference in rate of progression is perhaps the starkest component of heterogeneity, with post-diagnosis survival ranging from less than a year to more than 10 years. Most clinical trials do not formally incorporate progression rate as an inclusion criterion, though requiring that patients enroll within...
Improving therapy development in ALS centers, but for its ability to predict treatment—its ability to predict natural disease course in multiple combination of markers must be validated not only for personal communication). Any such marker or combination of diagnostic and progression biomarkers (Turner, analysis, and clinical assessments to develop a panel biomarker cohort study, employing MRI, biofluid number estimation (MUNE) (13), motor unit numbers being evaluated in this regard include motor unit itself allow shorter and smaller phase II trials. Markers being evaluated in this regard include motor unit number estimation (MUNE) (13), motor unit number index (MUNIX) (14), and electrical impedance myography (EIM) (15). Another early effort, the Oxford Study for Biomarkers in Motor Neurone Disease (BioMOX) is a multimodal, longitudinal biomarker cohort study, employing MRI, biofluid analysis, and clinical assessments to develop a panel of diagnostic and progression biomarkers (Turner, personal communication). Any such marker or combination of markers must be validated not only for its ability to predict natural disease course in multiple centers, but for its ability to predict treatment-dependent changes in clinical outcomes in eventual phase III trials.

Biomarkers of early disease may be especially important in future clinical trials, since it remains an open question whether instituting therapy at later stages can succeed, or instead whether there is a ‘point of no return’ in disease progression, beyond which virtually all potential therapies are likely to fail. Certainly, in neurodegenerative diseases in general and ALS in particular, increasing emphasis is being placed on studying patients earlier in their disease or, in the extreme, in the presymptomatic phase of disease. It is assumed, but has not been demonstrated, that a therapy is more likely to be beneficial if given during these early phases.

Whether a disease pathway is common to all ALS patients or limited to a subset, identifying a target within it remains the sine qua non of rational drug development. New genes and disease models should bring the field new insights into such pathways in the near future, with target identification and candidate drug development following quickly. In the simplest terms, a drug must meet three conditions (often called the ‘three pillars’) to have a chance of being effective: it must reach its target, interact with it, and trigger some downstream physiologic effect (16). Evidence that each of these three events occurs in humans greatly increases confidence that a drug will offer clinical benefit. Absence of such evidence increases the risk of failure during clinical development, and greatly decreases the likelihood that pharmaceutical companies will commit the substantial resources required to develop a drug. To date, no trial in ALS has had evidence that all three conditions have been met; indeed, relatively few trials have begun with identified molecular targets, and even fewer have had evidence that the target was either reached or engaged. This is not a challenge unique to ALS, as tools to identify central nervous system targets in general are only recently becoming available.

Development of target-specific biomarkers in parallel with putative new therapies is beginning to be seen as a threshold requirement for clinical testing in ALS. A key benefit of that requirement is that it has the potential to make even a negative phase II trial vastly more informative than has been the case in the past. For example, a PET ligand for the EAAT2 glutamate transporter is currently in the late stages of development (Sattler, personal communication). In a trial of a drug that is intended to up-regulate the transporter (as ceftriaxone has been shown to do in animal models), the ligand would have the potential to determine if the drug had achieved its intended downstream effect – namely, increasing the number of glutamate transporters.

The best hope for success in the future is to find appropriate drug activity biomarkers and evidence of target engagement as a component of the trial design. While a positive effect on survival would be the unmitigated success the field is looking for, a
negative result would also be valuable in reprioritizing drug development in other directions. With the appropriate tools in hand, an ideal scheme for development might be a phase IIa trial testing target engagement in a cohort enriched with the target in mind, followed seamlessly by a phase IIb trial to rapidly determine if engagement leads to improvement in a clinically relevant outcome, followed by a phase III trial.

One cautionary note should be made with regard to this scheme. It suggests that success will follow if only the ‘right’ target is found and engaged. However, it remains to be proved that engagement of a single target can have a beneficial effect in ALS. It may instead be the case that slowing the disease course can only be accomplished by hitting several targets at once (or sequentially) either with a single agent, or a combination of several. In this regard, it is worth noting that riluzole has multiple actions, and that there is no consensus on whether its benefit in ALS can be attributed to just one. If this is the rule in neurodegenerative disease, rather than the exception, it suggests that single-target drug development is facing a hidden hurdle that will be even harder to overcome than presently appreciated (and may help account for failure of phase III trials). Discovering pharmacodynamic markers for several putative mechanisms at once makes the challenge even greater.

How can the ALS trial community better serve patients?

At the same time as the trials community increases the rigor with which it approaches trial design, it should be sure not to lose focus on patient needs and experiences within the trial process. There are several potential areas for improvement. A significant opportunity lies in the development and expansion of telemedicine to clinical trials. Currently, patients wishing to participate in a trial usually must return to the clinical center for monitoring, entailing costs and inconvenience in the best of cases. In-home telemedicine visits, with caregivers trained to assist in administering the standard clinical measures used in trials, such as the ALSFRS and perhaps ventilatory function, are possible and may be practical for many trials, and would likely lower the barrier to enrollment, especially for patients who live far from their treatment center. That may be especially beneficial for non-intervention trials (i.e. those not testing a putative therapy), in which there is no potential for therapeutic improvement. Also, patients can and should be asked more often about which outcome measures would be most relevant to them; these are often quality-of-life endpoints, and incorporating them may increase patients’ sense that the trial is focused on their needs, and may reveal treatment benefits that clinicians have previously overlooked.

Current regulations in all countries emphasize the paramount importance of establishing that humans will not be exposed to unreasonable risk before a new treatment can be tested in a clinical trial. While recognizing that importance, those affected by ALS often become frustrated with the pace of regulatory approval for new trials, making the argument that their disease is a more certain danger than a putative treatment is likely to be. There is no simple answer to balancing safety risks with the urgency of finding new therapies, but a recognition that patients may be willing to accept a higher level of risk may help clinical researchers and regulatory authorities as they examine risk/benefit calculations for new agents. At the same time, patients are often dismayed by the requirement for a placebo arm in drug trials, as it lowers the odds of receiving a potentially helpful new treatment. One option proposed for reducing the size of the placebo arm in the earliest phases of development is to supplement it with data from historic controls. However, because of the evolving standard of care in ALS, data from older studies are unlikely to offer a valid comparison group for current trials. An alternative is to use a 2:1 ratio of active treatment to placebo. It is important to note that therapy development in general is accelerated by conducting well-designed studies, which include the use of appropriate controls. As was seen in the minocycline trial, some active treatments may be harmful, and patients in the placebo arm have a better outcome (17). Whatever the specific trial design, clinicians have the obligation to take time to discuss with patients and families the reasons behind the structure of trials, including placebo arms, blinding, the primacy of safety, and others.

Understanding the complexity of these issues is critical to recruitment, retention, and patient satisfaction. Managing expectations is also important. At this stage in the understanding of disease pathophysiology, treatments are not expected to cure ALS even if they are successful in slowing the disease or improving symptoms. It is critical that patients and families have a realistic understanding of what to expect in a trial. Finally, clinical researchers can advocate with sponsors to offer open-label access for trial participants once the blinded phase of the trial is complete, assuming a positive result from early analysis.

Independent of issues in trial design, actively engaging patients in the research process serves both the search for new treatments and the desires of patients to contribute to that effort. The importance of that active engagement extends beyond clinical trials. Enrolling in a data registry or contributing to a specimen bank are contributions every patient can make, and are contributions that may have as much importance in the ultimate development of a successful therapy as participation in a drug trial.
Summary
We recommend that future phase II clinical trials in ALS proceed when the proposed treatment is directed at targets that are likely to be involved in ALS pathogenesis in a defined subgroup of patients, and be accompanied by one or more biomarkers to track both clinical progression and pharmacodynamic engagement of the target. Innovations in trial structure, including centralized IRBs and master contracts, can help reduce the lag between approval and enrollment, and innovations in trial design can be used to accelerate transitions to later stages in drug testing for agents that demonstrate success early on. We recommend that trial leaders, in consultation with regulators and patient advocates, explore ways to enroll more patients, meet their needs better, and continue to balance risk and potential benefits in trials. Together, these steps have the potential to lead to trials with the highest likelihood of success.

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