HHS Public Access

Author manuscript

Nat Rev Neurol. Author manuscript; available in PMC 2016 December 26.

Published in final edited form as:

Nat Rev Neurol. 2015 February ; 11(2): 72–74. doi:10.1038/nrneurol.2014.250.

Motor neuron disease in 2014: Biomarkers for ALS—in search of the Promised Land

Adriano Chiò and

'Rita Levi Montalcini' Department of Neuroscience, University of Torino, via Cherasco 15, 10126 Torino, Italy

Bryan J. Traynor

Neuromuscular Diseases Research Unit, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD 20892, USA

Abstract

The past year has seen some extraordinary activity in clinical amyotrophic lateral sclerosis (ALS) research. Two trials were completed, with negative results, but the discovery of novel ALS-associated genes, and body fluid and imaging biomarkers warrants cautious optimism. Here, we provide a snapshot of some of the main findings in 2014.

2014 saw the completion of two highly anticipated clinical trials in amyotrophic lateral sclerosis (ALS).1, 2 The first one was a multistage, multicentre trial on ceftriaxone.1 Ceftriaxone was chosen on the basis of preclinical data from the SOD1 Gly93Ala mouse model of ALS, which indicated that cephalosporins enhance excitatory amino acid transporter 2 activity, delay disease onset and prolong survival.1 Patients treated with ceftriaxone in phase I (pharmacokinetics) and phase II (safety) sections of the trial showed slower decline in the revised Amyotrophic Lateral Sclerosis Functional Rating Scale than did patients receiving placebo. Alas, phase III (efficacy) failed to show a beneficial effect for the drug in primary endpoints of functional decline and survival. Nevertheless, the innovative trial design of the study, incorporating early and late stage testing (with appropriate go–no-go decision points), offers a useful model for future ALS clinical trials to move candidate therapeutic agents along the drug development pipeline more rapidly and efficiently.

The second trial was a placebo-controlled phase II–III trial of olesoxime (cholest-4-en 3-one, oxime; Trophos, France), a molecule with potential neuroprotective properties. Olesoxime was identified in an in vitro screen for compounds that protect motor neurons from death by trophic factor deprivation.2 This double-blind, randomized, placebo-controlled multicentre trial involved 512 patients with ALS across five European countries. Although the drug was found to be well tolerated by the patients, none of the primary or secondary end points were reached.

Corresponding author. Correspondence to: Adriano Chiò.

These negative clinical trials have led to substantial soul-searching among the ALS research community. Moving forward, the key questions centre on whether a better way to select agents to be brought forward for clinical trials can be found, and whether ALS clinical trial designs can be made more efficient. The first question is complex and beyond the scope of this article—instead, we will focus on growing efforts to develop reliable biomarkers for ALS.

Finding a biomarker that is specific to ALS, has excellent prognostic value, and is sufficiently sensitive to detect progression is challenging. There is, however, reason for cautious optimism as recent technological advances have enabled a more data-driven approach in the quest for a reliable ALS biomarker. The past year, in particular, has seen progress in a range of areas, including development of molecular biomarkers (genes, proteins, metabolic products), neurophysiological biomarkers (measurement of upper and lower motor neuron involvement), neuropsychological biomarkers (quantification of subtle cognitive impairment), and neuroimaging biomarkers (differentiation of ALS from disorders that mimic ALS; following the course of neurodegeneration).

During 2014, three novel ALS-associated genes were identified: MATR3,3 CHCHD10,4 and TUBA4A,5 and more are on the way. These genes provide insight into potential pathogenetic mechanisms in ALS. MATR3, located in 5q31.3, encodes matrin 3 protein—which is a nuclear matrix protein bound to the inner nuclear membrane—and is involved in DNA repair and transcription, and RNA processing and transport.3 CHCHD10, located in 22q11.23, encodes a coiled-coil helix–coiled-coil helix protein the function of which is still unknown. However, CHCHD10 belongs to a family of mitochondrial proteins that are located in the intermembrane space; some of these proteins are involved in cristae integrity and mitochondrial fusion.4 TUBA4A, located in 2q36.1, encodes tubulin alpha 4A protein. Functional analyses revealed that mutant forms of TUBA4A destabilize the microtubule network and diminish its repolymerization capability; these findings emphasize the role of cytoskeletal defects in ALS.5 Overall, in approximately two-thirds of familial ALS cases and 10% of apparently sporadic cases, a genetic cause is detectable; the rest of the aetiology remains unknown.3 In theory, the detection of a mutation in a patient with suspected ALS should represent a specific and sensitive diagnostic marker. The reality is different, as the pathogenicity and penetrance of many variants in these genes are not fully determined; moreover, some cases of ALS might be oligogenic, that is, the phenotype is determined by the interaction of more than one gene.

Other 'wet' biomarkers have also shown promise in ALS diagnostics. Serum levels of light chain neurofilaments—major structural proteins in neurons that are released following neuronal damage—were recently shown to have >90% sensitivity and specificity for separating patients with ALS from healthy controls.6 Moreover, the immunoreactivity to plasma light chain neurofilaments changes in relation to ALS clinical staging, indicating that this biomarker might be also be useful in monitoring disease progression.6 The ratio between phosphorylated tau (p-tau) and total tau (t-tau) in cerebrospinal fluid is similarly reported to have >90% sensitivity and specificity for distinguishing ALS from patients with 4-repeat-tau diseases (progressive supranuclear palsy and corticobasal degeneration); furthermore, the p-tau:t-tau ratio in patients with ALS correlated with clinical measures of

disease severity.7 Although these findings are promising, neither study compared patients with ALS with patients with diseases that mimic ALS, such as primary lateral sclerosis, cervical myelopathy, or axonal polyneuropathies. Therefore, these studies do not provide definitive proof that light chain neurofilaments or tau can be used as reliable diagnostic tools. Furthermore, longitudinal studies are necessary to determine whether these biomarkers are useful as proxies of ALS progression.

Neuroimaging is another rapidly evolving field of ALS research, and is being driven by improvements in imaging techniques and data analysis. Brain MRI has provided remarkable insight into upper motor neuron degeneration and the involvement of extramotor areas, such as the prefrontal cortex and basal ganglia. In an innovative approach to the analysis of neuroimaging data, 29 patients with ALS and 30 healthy controls matched for age and sex underwent multimodal brain MRI that included proton magnetic resonance spectroscopy (MRS) with spectral editing techniques to measure γ-aminobutyric acid, and diffusion tensor imaging (DTI) to measure fractional anisotropy of the corticospinal tract.8 The diagnostic accuracy was markedly improved when the MRS data were combined with the DTI data, as compared with use of only the DTI data.

Although there is growing optimism concerning the use of imaging as a biomarker of progression, several obstacles remain. The most obvious—and perhaps the most difficult to overcome—is the high attrition rate among patients with ALS in neuroimaging studies: respiratory compromise in the later stages of disease means that patients cannot lie flat for the prolonged periods needed to complete these advanced imaging examinations. The second issue surrounds the availability and cost of installing these advanced imaging modalities outside of academic centres.

18F-FDG–PET could be an alternative to multimodal MRI. Two large independent studies have shown that PET has a >90% accuracy for differentiating ALS patients from healthy controls,9, 10 and from patients with primary lateral sclerosis.10 The most important clusters of discrimination were found bilaterally in the thalamus, primary motor cortex, striatum, prefrontal and lateral prefrontal cortex, and posterior cingulate. The value of 18F-FDG–PET as a prognostic marker has not yet been studied, but a practical advantage of this modality is the shorter scan time relative to MRI.

ALS biomarkers are not yet available, but the scientific literature over the past year is perhaps grounds for cautious optimism (Table 1). A reliable biomarker would improve the efficacy of ALS clinical trials in several ways. First, such a biomarker could identify fast and slow progressors among patients, thereby enabling more-refined stratification and statistical analysis. Second, it would increase trial power, thereby decreasing the number of patients required and notably reducing the duration of the trial. The subsequent decrease in the cost of trials and would make the drug development pipeline more nimble. Third, and probably most importantly, a reliable biomarker would provide a more objective, quantitative end point compared with the clinically based outcomes currently used in ALS trials.

Acknowledgments

Competing interests statement

A.C. serves on scientific advisory boards for Cytokinetics, Biogen Idec, and Italfarmaco. B.J.T. holds a patent on methods to screen for the hexanucleotide repeat expansion in C9ORF72.

A.C. is currently funded by Italian Health Ministry grant RF-2010-2309849, European Community's Health Seventh Framework Programme (FP7/2007–2013) under grant agreements 259867 and 278611, and the Joint Programme-Neurodegenerative Disease Research granted by Italian Ministry of Health (Sophia Project) and by Italian Ministry of University and Research (ALS-CARE and Strength Projects). B.J.T. is currently funded by intramural Research Programs of the US National Institutes of Health (NIH), National Institute on Aging (Z01-AG000949-02) and NINDS.

References

1. Cudkowicz ME, et al. Safety and efficacy of ceftriaxone for amyotrophic lateral sclerosis: a multi-stage, randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2014; 13:1083–1091. [PubMed: 25297012]
2. Lenglet T, et al. A phase II–III trial of olesoxime in subjects with amyotrophic lateral sclerosis. Eur. J. Neurol. 2014; 21:529–536. [PubMed: 24447620]
3. Johnson JO, et al. Mutations in the Matrin 3 gene cause familial amyotrophic lateral sclerosis. Nat. Neurosci. 2014; 17:664–666. [PubMed: 24686783]
4. Bannwarth S, et al. A mitochondrial origin for frontotemporal dementia and amyotrophic lateral sclerosis through CHCHD10 involvement. Brain. 2014; 137:2329–2345. [PubMed: 24934289]
5. Smith BN, et al. Exome-wide rare variant analysis identifies TUBA4A mutations associated with familial ALS. Neuron. 2014; 84:324–331. [PubMed: 25374358]
6. Gaiottino J, et al. Increased neurofilament light chain blood levels in neurodegenerative neurological diseases. PLoS ONE. 2013; 8:e75091. [PubMed: 24073237]
7. Grossman M, et al. Phosphorylated tau as a candidate biomarker for amyotrophic lateral sclerosis. JAMA Neurol. 2014; 71:442–448. [PubMed: 24492862]
8. Foerster BR, et al. Multimodal MRI as a diagnostic biomarker for amyotrophic lateral sclerosis. Ann. Clin. Transl. Neurol. 2014; 1:107–114. [PubMed: 25356389]
9. Pagani M, et al. Functional pattern of brain FDG-PET in amyotrophic lateral sclerosis. Neurology. 2014; 83:1067–1074. [PubMed: 25122207]
10. Van Laere K, et al. Value of 18fluorodeoxyglucose-positron-emission tomography in amyotrophic lateral sclerosis: a prospective study. JAMA Neurol. 2014; 71:553–561. [PubMed: 24615479]

Key advances

- The ratio between phosphorylated tau and total tau in the cerebrospinal fluid could be a diagnostic and prognostic biomarker in amyotrophic lateral sclerosis (ALS)7
- Multimodal MRI that combines magnetic resonance spectroscopy and diffusion tensor imaging can markedly improve differential diagnosis between patients with ALS and healthy controls8
- Two studies suggest 18F-FDG–PET to be a feasible tool for ALS diagnosis with the ability to distinguish ALS from disorders with similar symptoms (e.g. primary lateral sclerosis)9, 10
- Reliable biomarkers for ALS could improve patient stratification, increase statistical power and provide quantitative end points, thereby facilitating the efficacy of clinical trials

Table 1

Diagnostic and prognostic biomarkers for ALS emerging in 2014

Biomarker	Diagnostic value	Prognostic value	Problems/limitations
ALS-related genes	Yes	Usually no, with some exceptions (e.g. *SOD1* Ala4Val)	Oligogenicity; the pathogenicity of some mutations is uncertain; scarce phenotype–genotype correlation
Neurofilaments in blood	Yes, but ability to distinguish ALS from ALS mimics not tested	Yes, but limited data	Not yet known
Phosphorylated tau in CSF	Yes, but ability to distinguish ALS from ALS mimics not tested	Yes, but limited data	Serial measurements of CSF are unlikely to be obtainable
Multimodal MRI	Yes, but ability to distinguish ALS from ALS mimics not tested	Not tested	Serial MRI scans are unlikely to be obtainable
^{18}F-FDG–PET	Yes, to be confirmed in larger multicentre studies	Not tested	Not yet known

Abbreviations: ALS, amyotrophic lateral sclerosis; CSF, cerebrospinal fluid; SOD1, superoxide dismutase 1.