Major advances in amyotrophic lateral sclerosis in 2020

Amyotrophic lateral sclerosis (ALS), a heterogeneous syndrome recognised clinically as a progressive degeneration of the upper and lower motor neurons, is traditionally classed as a neuromuscular disorder. However, major advances in cell and molecular biology, neuroimaging, neuroelectric signal analyses, and neuropathology have categorically shown that ALS should be considered to be a neurodegenerative disorder, albeit with a substantial neuromuscular component.[1] Although the biological processes underlying the pathogenesis and progression of the disease are multifactorial, there is increasing evidence that ALS is characterised by early cortical hyperexcitability with altered synaptic integrity, possibly mediated by the deposition of TAR DNA-binding protein 43 (TDP-43),[2] followed by more widespread disruption of neuronal networks.[3]

These insights provide multiple potential targets for drug development, although it is likely that different pathogenic mechanisms will ultimately require a precision medicine approach to therapeutics. The immediate challenge will be to provide tools that can discern ALS subtypes and to align these with new therapeutic approaches.

For more on **TRICALS** see https://www.tricals.org/

This year also saw the launch of the Treatment Research Initiative to Cure ALS (TRICALS). TRICALS's position paper describes the major barriers that impede the translation of therapeutics from promising pre-clinical studies to successful pivotal phase 3 studies.[4] They suggest that overcoming these barriers will require better biomarkers for biological activity and target engagement; improvement of eligibility criteria for trials using statistical models that incorporate multiple prognostic factors; innovative trial designs (eg, using a platform design with a master protocol, multiple therapeutic groups, and a shared placebo group); and better quantitative outcome measures that address the current limitations of the Revised ALS Functional Rating Scale (ALSFRS-R).

2020 has seen important milestones in each of these areas, including the identification and development of a range of promising biomarkers (eg, neurofilaments, chitinase proteins, and non-coding RNA biomarker signatures). A series of sophisticated neuroimaging and advanced neurophysiological techniques have begun to characterise the extensive extra-motor network disruption,[5,6] and studies of pre-symptomatic patients carrying known variants show that cortical disruption occurs many years before discernible clinical symptomatology.[7] These technologies could be harnessed as sensitive markers of early pathology, and could also be developed to address the limitations of current trials, which have generally excluded measures of cognitive and behavioural change.

Notwithstanding these advances, the syndrome of ALS remains a recognisable, albeit heterogeneous, clinical entity. There have been many attempts to simplify the diagnostic characterisation of ALS to facilitate more uniform enrolment in clinical trials. The El Escorial diagnostic criteria—in which cases are categorised as possible, probable, or definite ALS—are unwieldly, and rigid application has excluded some patients with ALS who might otherwise have been eligible for the many clinical trials that are underway. The publication of new consensus diagnostic criteria this year provided a welcome simplification.[8] The Gold Coast criteria require the presence of progressive motor impairment; the presence of upper and lower motor neuron dysfunction in at least one body region, or lower motor neuron dysfunction in at least two body regions; and investigations that exclude other disease processes. The Gold Coast criteria recognise the extra-motor domains of ALS, but do not require their presence for diagnosis.

Providing diagnostic clarity for ALS is important, as the past year has witnessed a veritable explosion in trials of promising therapeutics, including gene-based therapies, repurposed combinations of drugs, and novel compounds that target specific pathways.

An early-phase trial of an intrathecal antisense oligonucleotide therapy, tofersen, against variants in superoxide dismutase 1 (*SOD1*) found that the highest dose of tofersen was associated with reductions in CSF SOD1 concentration and CSF neurofilaments.[9] A phase 3 study is now planned, which, if positive, will herald the first effective precision medicine-based disease-modifying therapy for ALS. Additional gene-based therapies are in the early clinical and preclinical phases, and include antisense oligonucleotides for ALS and frontotemporal dementia associated with C9orf72, and antisense oligonucleotides for the genetic modifier Ataxin-2, which modulates TDP-43 expression.

Repurposed drugs for ALS are also of increasing interest, as evidenced by promising results from a phase 2 double-blind placebo-controlled study of AMX0035.[10] This combination of sodium phenylbutyrate and taurursodiol was designed to prevent neuronal death by simultaneously mitigating endoplasmic reticulum stress and mitochondrial dysfunction. The mean rate of decline in ALSFRS-R total score was significantly slower with AMX0035 than with placebo. A separate phase 3 study of taurusodiol versus placebo is underway in Europe, and it is likely that an additional phase 3 trial of AMX0035 will be initiated in 2021.

Finally, the impact of the COVID-19 pandemic on clinical research in ALS has been considerable. There has been a significant shift to remote monitoring using telemedicine, as reflected in numerous publications over the past 6 months. COVID-19 has also necessitated a paradigm shift for the future design and execution of clinical trials, with a change in emphasis from in-clinic evaluation to home monitoring. Home monitoring opens opportunities for repeated testing of defined outcomes over shorter periods, providing a richer dataset of outcome measures that could, in future, reduce variance and improve reliability.

OH is the editor-in-chief of the journal *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, and has consulted for Cytokinetic, Wave Life Sciences, Novartis, Orion, and Denali.

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Sleep research in 2020: COVID-19-related sleep disorders

2020 has been an unprecedented year because a modified coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), spread rapidly from China to all continents, leading to the COVID-19 pandemic. The first studies of COVID-19-associated sleep disorders were reported in China. Huang and Zhao[1] collected information from a survey of 7236 volunteers (mean age 35·3 years [SD 5·6]). About a third of them were health-care workers. About 35% of these participants reported symptoms of general anxiety, 20% of depression, and 18% of poor sleep quality.[1] The participants who were most worried about the pandemic also reported the most symptoms. Health-care workers were clearly under great pressure, which was reflected in the high prevalence of mental-health symptoms that they reported.[1]

The increased prevalence of sleep disorders in 2020 has also been highlighted in several other publications from different countries. These studies examined the effect on sleep of SARS-CoV-2 infection and confounders related to isolation, quarantine, anxiety, stress, or financial losses. According to a European task force, symptoms of insomnia could be related to psychosocial factors and to the confinements.[2] In Italy, anxiety related to COVID-19 was highly associated with disturbed sleep. In a survey of 2291 Italians, 57·1% reported poor sleep quality, 32·1% high anxiety, 41·8% high distress, and 7·6% reported post-traumatic symptoms of stress.[3] In the International COVID-19 Sleep Study,[4] different factors are being investigated using a harmonised set of questions. Insomnia, nightmares, sleep apnoea, fatigue, exhaustion, and REM sleep behaviour disorder are being investigated by this collaboration.[4] The hypothesis is that fatigue, sleepiness, and REM sleep behaviour disorder might be related to SARS-CoV-2 infection per se, whereas insomnia might be related mainly to confinement, anxiety, and other psychosocial factors.[2]

Although studies related to COVID-19 have dominated the field in 2020, other important investigations have