Improving clinical trial outcomes in amyotrophic lateral sclerosis

About Amyloid lateral sclerosis (ALS):

Deconstructing ALS: ALS is often identified by abnormalities in nerve cells (neurons) involving the brain, spinal regions and muscles connected to these neurons. Approximately 15% of ALS cases are familial (inherited through genetics). The remaining 85% of cases belong to sporadic cases (cases with no known family history of the disease).

Development of therapeutics:

In light of the diversity in characteristics of ALS within patients, tailored therapeutics, based on an individuals’ genetic feature has begun to emerge. Such an approach has the potential to be a more targeted and therefore effective therapeutic strategy for patients. This may prove more effective than the once size fits all medicine previously used.

One size fits all medicine: Is the use of a single treatment for a heterogenous population (a population where every member has a different characteristic, for example, type of ALS and age). Within this treatment method, some patients benefit from the treatment and some do not.

Stratified medicine: This is an improvement in the ‘one size fits all medicine’ by separating the patients by demographic, for example, the type of ALS. Resulting in a more tailored therapeutic.

Precise medicine: This is to look at an individual’s genetic features as a guide to developing a more personalised therapy, resulting in more patients benefiting from tailored treatment.

How to achieve precise medicine:

Biomarkers: In order to understand differences in response to a trial therapy, reliable biomarker are required. Biomarkers are a measurable indicator of a biological state or condition within the body, allowing the evaluation of biological processes.

Currently, biomarkers are used in ALS clinically to indicate the loss of upper or lower motor neurons, allowing the monitoring of disease progression within patients.

Biomarkers can also be used to diagnose ALS, such as the case for cortical hyperexcitability (the overproduction of electrical signals within the brain and muscles).

There are other methods of observing ALS disease progression, e.g. MRI (magnetic resonance imaging, allows imaging of the anatomy and physiological processes of the body). However, the sensitivity of these measurements can be inconsistent.

The most promising biofluid marker of ALS is the protein neurofilament, which is found in the cerebrospinal fluid (A fluid that surrounds the brain and spinal cord) and blood. Levels of this protein correlate with disease progression, allowing the patients’ progression to be measured accurately. This monitoring could lead to the progression of treatments that are refined and tailored to the individual patient, enabling decisions regarding potential therapeutic agents to be made earlier.

Limitations and future of biomarkers: The development of biomarkers for trials is complicated due to ALS being caused by changes to multiple pathways. This means that multi drug trials will be needed to tackle different causes of the disease. However, biomarkers may allow these areas to be targeted more effectively.

Due to the nature of ALS, it is difficult to predict disease onset, if a patient does not have a family history of the disease. Despite this, the use of predictive biomarkers does exist as expansion derived peptides (molecules that act as structural components of cells, tissues, hormones, toxins, antibiotics and enzymes) from ALS causing genes was present within the cerebrospinal fluid and blood mononuclear cells (blood cells that have a
single round nucleus) many decades before symptoms onset. This means that biomarkers could help early diagnosis or diagnosis predictions may be more effective.

**Drug repurposing:** This is the repurposing of existing drugs, to enable a rapid assessment of drug efficiency in phase 2 trials (the part of the test which further assesses the safety and effectiveness of a drug) due to the drug safety already being known.

The use of drug repurposing has enabled advances in cell reprogramming (turning adult specialised cells into a cell type that can become any cell that is required). Human somatic cells (any cell in the body except sperm and egg cells) have been reprogrammed into pluripotent stem cells, which can then be ultimately converted into nerve cells and glial cell (non-neuronal cells within the central nervous system) lines, allowing for the possible replacement of dead nerve cells.

The use of existing drugs that modulate established pathophysiological mechanisms (the mechanisms involved in disordered physiological processes, resultant from disease or injury) in ALS has identified several therapeutic and medical candidates. The most promising of these are as follows: Edaravone, Ezogabine, Immunomodulatory therapies (therapies/medications that help regulate/normalize the immune system), AMX0035, Rasagiline, Arimoclomol, High-throughput drug screening, Genetic and cellular therapy, Antisense oligonucleotides, Gene editing and cellular therapy.

**Improving trial design:** Current trials in ALS and other neurodegenerative diseases, is conducted through randomized controlled trials. This is where the effect of a therapeutic is compared to a placebo (a substance that has no therapeutic effect, used as a comparison for trial drugs/therapeutics). These trials are often costly and inefficient, as only a small proportion make it from initial testing to the commercial market.

**Advanced trial design:** Aims to maintain the rigour of randomized controlled trials while maximising efficiency, reducing cost and providing answers regarding efficacy. One such way this is achieved, is through the use of a master protocol for the simultaneous evaluation of multiple compounds. These trials have found success when used in cancer, HIV and some neurological diseases.

In multi-arm multi-stage trials, eligible patients are randomly assigned one of four sub study groups and whether they receive a placebo or not. The master protocol determines the selecting criteria for patients’ e.g. genetic features. This allows comparison between treatments and patients, in order to find the most effective treatment for different demographics.

**Patient stratification:** Allows the study of patients before the trial randomly assigns treatment. This means that more accurate indications of disease progression within an individual may be monitored, allowing the drug efficiency/effectiveness to be seen more clearly. This may result in more accurate tailored treatment.

**Patient report outcomes:** This is where patients report their outcomes from the trial to the researchers, allowing for more feedback and data to be collected. This will aid the trials process, as many possible trial candidates are restricted by lack of access to the clinical trial. This is due to travel difficulties or poor adherence in ALS clinical trials. These types of trials are useful, as they allow an insight into personal well-being, which is not often seen in other approaches. Despite this, there are limits, as some people may be unfamiliar with such digital platforms to provide feedback and lack objectivity when describing their experience.

**Conclusion:**

ALS is a complex neurodegenerative disorder. Consequently, effective treatment strategies might require different compounds acting in synergy, potentially at different stages of the disease. Advanced clinical trials seem critical to accelerating the development of such novel therapies in to advanced clinical trials. The implications of more advanced clinical trials could shorten trial duration, reducing both the cost and the burden to patients. Ultimately, this would provide hope that effective therapies can be developed for future use in the ALS clinic.