Detecting drug effects in ALS patients using electrophysiological biomarkers

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Ethical review	Approved WMO
Status	Pending
Health condition type	Neuromuscular disorders
Study type	Observational non invasive

Summary

ID

NL-OMON56704

Source
ToetsingOnline

Brief title
Electrophysiological biomarkers in ALS patients

Condition

- Neuromuscular disorders

Synonym
ALS, Amyotrophic Lateral Sclerosis

Research involving
Human

Sponsors and support

Primary sponsor: Neurologie
Source(s) of monetary or material Support: ALS Stichting

Intervention

Keyword: Amyotrophic Lateral Sclerosis, Drug development, Electrophysiological biomarkers

Outcome measures

Primary outcome

Excitability measures of the peripheral nerve. Several distinct measurements will provide in-debt information regarding the functioning of different ion-channels.

Secondary outcome

Excitability measures of the peripheral nerve. Several distinct measurements will provide in-debt information regarding the functioning of different ion-channels. CMAP (compound muscle action potential)-scan, to determine number of functional motor units, their size and stability.

Riluzole and neurofilament assessment (in blood). Clinical tests (eg. lung capacity, strength assessment in the hand, neurological clinical assessment, ALS questionnaire

Study description

Background summary

Amyotrophic Lateral Sclerosis (ALS) is a devasting and fatal motor neuron disease, affecting the upper and lower motor neurons. This results in progressive loss of muscle function, which eventually leads to the loss of respiratory muscle function and death. Approximately 500 people are diagnosed with ALS each year in the Netherlands alone, and mean survival is three years after onset of symptoms. The disease can unfold at any age, but most often reveals itself in patients aged 50 to 75. Currently, patients are treated with Riluzole, a drug expanding life by an average of three months. Though Riluzole has been standard clinical practice for over two decades, its exact mechanism of neuroprotective effects remains unclear.

Current efforts to significantly slow down ALS and prolong patient survival have proven to be extremely difficult. Whilst only the most promising preclinical drugs are advanced to clinical trials, only about 1% of these are actually approved for use in clinical practice. A major challenge is the translation from preclinical results (e.g., gained from cellular models and/or animal experiments) to clinical results with patients. A key bottleneck is the inability to verify target engagement in patients early, meaning that it is often unclear whether the drug*s mechanism of action is different in patients from that what was observed in preclinical models. As such, researchers have no early determinants to assess if the target engagement is similar in patients. This forces investigators to rely on expensive clinical trials of long duration. Insensitive clinical endpoints, such as patient survival or functional loss, further complicates the assessment of a drugs effect and potential. New to this trial, we aim to investigate the feasibility of nerve excitability testing as a biomarker to assist in the translation between preclinical and clinical ALS medication development. Nerve excitability testing is a technique related to the clinical EMG, that assesses the excitability properties of axons of peripheral motor neurons. It is non-invasive and can be performed both in pre-clinical and clinical setting.

A frequently observed preclinical phenomenon of ALS is the altered excitability properties of central and peripheral motor neurons. Abnormal peripheral excitability properties have been suggested to be a result of altered ion channel functioning, including potassium and sodium channels. These alterations in ion channel functioning have been linked to ALS progression rate and survival, and can be mapped using nerve excitability testing. Explorative research illustrates that ALS-medications such as Riluzole can alter the nerve excitability properties in ALS patients, with significant results four weeks after initiation of Riluzole. This study was however explorative. In this study, we will therefore aim to develop a detailed protocol for assessing ion-channel changes induced by Riluzole in ALS patients, using nerve excitability testing. We aim to gather enough data to build a translational tool capable of assisting researchers in search of a cure for ALS. In future research, we could further obtain the available preclinical data of published meta-results showing effects of Riluzole on motor neuron excitability, integrating them into a translational preclinical-to-clinical framework. If this proves successful, this model could assist in future drug development.

Study objective

Main objective is to determine whether nerve excitability can detect drug-induced effects of Riluzole in yet treatment- naïve patients with ALS. Secondary objectives are to determine the correlation between the Riluzole plasma concentration levels and motor nerve excitability indices, to assess the effect of Riluzole use on neurofilament levels, to investigate their relationships with the disease course in patients with ALS and to determine the

diagnostic value of nerve excitability and CMAP scan assessments.

Study design

Observational longitudinal design with 115 study subjects:
- 25 MND-suspected patients, without a definitive ALS diagnosis after their diagnostic day
- 50 newly diagnosed ALS patients starting on Riluzole

Furthermore, we will examine 40 healthy controls in a mainly cross-sectional setup, as reference to pathological changes.

Study burden and risks

The risks associated with study participation are very slim. Nerve excitability testing and the CMAP scan have been used in previous METC-approved clinical studies, using a total of hundreds of study subjects without any harmfull complications. Some study subjects have experienced a slight local reddening of the skin, which has always been temporary. Nearly all study subjects do not find the scan painfull, but otherwise we can stop the measurements instantly. Some patients even fall asleep during the test.

During the collection of blood samples (for patients with ALS in part 2), it is possible to create a local hematoma. To minimise this chance, only experienced and qualified hospital staff will collect these samples.

Clinical tests involved in this study, e.g. the assessment of lung capacity, strength assessment of the hand, neurolocial clinical assessment and the ALS questionnaire, are without any risks.

Whilst the risks associated with participation in this trial are very slim, there is some burdens for patients, mostly in the additional visits associated with participation. After diagnostic day, we aim to assess patients five additional times. In order to minimise their hospital visits, we attempt to coïncide as many visits with their regular hospital visits as possible. We except that this is possible additional visits to the hospital can be reduced to 2-3 visits.

There are no clear benefits for the individual patients associated with participating in this study. However, if nerve-excitability proves to be suitable in detecting drug effects in our patients, it could speed up the development of future drugs. In such an instance, the ALS community will benefit directly from the results of this study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

In order to be eligible to participate in the study, a subject must meet the following criteria:
o Age >=18 years
o Written informed consent

For the first part (as part of the diagnostic process and treatment-naïve subjects):
o Patients with suspected MND
o No use of Riluzole medication
o Participation in the NMZ biobank (neuromuscular biobank from the UMC Utrecht)

For the second part (five serial electrophysiological follow-up recordings):

o Diagnosis of ALS, by either Gold Coast Criteria or El Escorial
o Routine use of Riluzole twice daily
o A measurable maximum CMAP >2mV in the abductor pollicis brevis (APB)

For the disease control group (single electrophysiological follow-up recording)
o Participation in first part (pre-diagnostic assessment)

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study (please refer to C1 document, 4.3):
- Exclusion of study participation according to the TRICALS profile risk calculator, a validated tool that screens patients for eligibility for ALS study participation for the five follow-up recordings
- Age <18 years
- Signs of other neuropathies than MND, i.e. carpal tunnel syndrome (CTS) at diagnostic work-up (part 1)
- The use of medication that can affect the peripheral nerve ion-channel currents (except for patients with ALS who use Riluzole within part 2)
- Any physical, psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol. Judgment is up to the investigators

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL
Recruitment status:	Pending
Start date (anticipated):	01-03-2024

Enrollment:	115
Type:	Anticipated

Ethics review

Approved WMO Date:	10-04-2024
Application type:	First submission
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL85420.041.23