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Analysing neuroinflammation and neurodegeneration in amyotrophic lateral sclerosis: quantitative imaging in a clinical trial

Submission date
25/10/2016

Recruitment status
No longer recruiting

Registration date
16/11/2016

Overall study status
Completed

Last Edited
16/06/2020

Condition category
Nervous System Diseases

[X] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Amyotrophic Lateral Sclerosis (ALS; also known as motor neuron disease) is an incurable disease of the nervous system which causes the movement or 'motor' cells that control the muscles in the body to die. This leads to weakness, muscle loss and death within 5 years. A drug called Riluzole is the only drug currently available to slow down ALS progression, but this can only prolong survival by a few months at most and so better treatments are urgently needed. The aim of this study is to use magnetic resonance imaging (MRI), a type of scan that produces detailed images of the inside of the body, to better understand the way in which nerve cells die in ALS, particularly the role that inflammation may have in the damage to the brain.

Who can participate?
Patients aged 18 to 75 with ALS participating in the MIROCALS study

What does the study involve?
The study runs alongside another study called MIROCALS which tests whether a low dose of a chemical called interleukin-2, which is used by cells in the immune system to signal to each other, can safely improve the survival times of patients with ALS. All patients participating in MIROCALS take standard Riluzole treatment for 3 months, then are randomly allocated into one of two groups: one group receives additional low dose interleukin-2 (ld-IL-2); the other receives additional placebo (dummy drug) treatment. A range of substances, called biomarkers, which relate to nerve cell damage and immune system function, are measured from patients' spinal fluid and blood, and the severity of their disease is assessed. This study recruits 50 patients from MIROCALS for MRI scanning at the start of the study (whilst on Riluzole only) and again 4-6 months after allocation to either additional treatment. The healthy volunteers only require one scan whereas patients with ALS have two scans roughly 5-7 months apart. The types of scan include Neurite Orientation Dispersion and Density Imaging (NODDI), which provides data on nerve cell density and the extent of their branching connections with other cells; quantitative magnetisation transfer (qMT) imaging, which measures primarily nerve cell insulation (myelin) content and composition; and resting state functional MRI (rsfMRI) to study the degree to which various brain regions communicate with each other at rest. The scans take about 50 minutes to

complete in total. The brain scans are then compared with similar brain scans from a group of healthy volunteers (recruited into a separate study called MultiNICS), and between the two groups of patients treated with either Riluzole and Placebo or Riluzole and ld-IL-2. The degree of change on the MRI scans is also compared to the levels of the biomarkers and measures of disease severity.

What are the possible benefits and risks of participating?
It is hoped that the study will yield vital clues as to the processes by which the brain becomes damaged in ALS and not only assist in the development of further treatments but assist with the design of future studies in this field. Some of the MRI techniques used are relatively new but are as safe as having a 'normal' MRI brain scan and none require any invasive tests such as injections.

Where is the study run from?
1. Princess Royal Hospital (UK)
2. Royal Sussex County Hospital (UK)
3. King’s College Hospital (UK)
4. The National Hospital for Neurology and Neurosurgery (UK)
5. The Royal London Hospital (UK)
6. Sheffield Royal Hallamshire Hospital (UK)

When is the study starting and how long is it expected to run for?
April 2017 to January 2019

Who is funding the study?
University of Sussex (UK)

Who is the main contact?
1. Dr Andrew Barritt
2. Prof. P Nigel Leigh

Contact information

Type(s)
Scientific

Contact name
Dr Andrew Barritt

ORCID ID
https://orcid.org/0000-0002-9723-6946

Contact details
Clinical Imaging Sciences Centre
Brighton & Sussex Medical School
University of Sussex
Falmer Campus
Brighton
United Kingdom
BN1 9RR

Type(s)

Scientific

Contact name
Prof P Nigel Leigh

Contact details
Clinical Imaging Sciences Centre
Brighton & Sussex Medical School
University of Sussex
Falmer Campus
Brighton
United Kingdom
BN1 9RR

Additional identifiers

Protocol serial number
BSMS-16-012-LEI; H2020/PHRC-N/2014/GB-01 Substantial Amendment 3

Study information

Scientific Title
Analysing Neuroinflammation and Neurodegeneration in Amyotrophic Lateral Sclerosis: Quantitative Imaging in a Clinical Trial

Acronym
ANNALS-QuICT

Study objectives
Current study hypothesis as of 24/03/2017:
1. Baseline parameters measured by the detailed magnetic resonance imaging (MRI) will be significantly different in patients with ALS compared to a group of healthy control subjects (recruited into a separate study called MultiNICS)
2. Baseline parameters in patients with ALS will be able to predict rate of progression and relate significantly to the 'intensity' of nerve cell damage & inflammation reflected by biomarker levels of, for instance, neurofilament proteins and inflammatory cytokines, respectively, as measured by the MIROCALS study
3. MRI parameters will demonstrate progression over time between the baseline and follow-up scan in patients with ALS
4. If the MIROCALS trial is positive, there will be greater progressive change in MRI parameters between baseline and follow-up in patients treated with Riluzole + placebo compared to Riluzole + ld-IL-2

Previous study hypothesis:
The main hypotheses are:
1. That parameters of neural disruption measured by the detailed magnetic resonance imaging (MRI) brain images, including Neurite Orientation Dispersion and Density Imaging (NODDI), quantitative magnetization transfer imaging (qMTi) and resting state fMRI (rsfMRI) sequences, will be significantly increased in patients compared to controls at baseline.
2. That the degree of disruption on MRI for each patient will be able to predict their rate of

disease progression and be significantly associated with 'intensity' of neurodegeneration and neuroinflammation reflected by biomarker levels of, for instance, neurofilament proteins and inflammatory cytokines, respectively, as measured in the MIROCALS study.
3. That changes in MRI indices between baseline and follow-up scans in patients will be reflected by changes in clinical progression, as well as their 'intensity' of neurodegeneration and neuroinflammatory measured by the MIROCALS biomarkers.

Ethics approval required
Old ethics approval format

Ethics approval(s)
London Central REC, 07/03/2017, ref: 16/LO/1004

Study design
Observational prospective case-control study

Primary study design
Observational

Study type(s)
Diagnostic

Health condition(s) or problem(s) studied
Motor neuron disease, also referred to as amyotrophic lateral sclerosis

Interventions
Current interventions as of 24/03/2017:
The "Analysing Neuroinflammation and Neurodegeneration in Amyotrophic Lateral Sclerosis (ALS): Quantitative Imaging in a Clinical Trial" (ANNALS-QuICT) study will perform detailed quantitative magnetic resonance brain imaging (MRI) on patients with ALS. ANNALS-QuICT is an ancillary study to a double-blind randomised placebo-controlled trial called MIROCALS and only UK patients enrolled into MIROCALS are eligible.

50 patients from MIROCALS will undergo baseline MRI scans and again 4-6 months after they have been randomised to treatment. The MRI techniques to be used include Neurite Orientation Dispersion and Density Imaging (NODDI) which provides data on nerve cell architecture and density; quantitative magnetisation transfer (qMT) imaging which provides measures primarily about nerve cell insulation (myelin) content and composition; and resting state functional MRI (rsfMRI) to study the degreeto which brain regions communicate at rest.

The principal brain regions of interest for analysis will be the brain surface controlling movement (primary motor cortices), the projection of these fibres into the spinal cord (corticospinal tracts), a major connection between the two brain hemispheres (the corpus callosum) and a known resting state (sensorimotor) network, although whole brain analyses will be possible with the extensive imaging data acquired.

There is no active intervention or additional follow-up as the parent trial MIROCALS will do this over 18 months and share its data with ANNALS-QuICT.

Previous interventions:
This is an ancillary study to a double-blind randomised placebo-controlled trial called MIROCALS,

which will perform detailed quantitative MR brain imaging on a proportion of patients enrolled into MIROCALS along with a healthy age-matched control group

This project will use detailed quantitative magnetic resonance imaging (MRI) to understand the mechanisms of the neurodegeneration in ALS, particularly the role of neuroinflammation in this process. The project will run in the context of a unique double-blind, randomised controlled trial called MIROCALS (Modifying Immune Responses and Outcomes in ALS) using low dose interleukin-2 (ld IL-2) to increase white blood cells known as regulatory T-cells (Tregs). Treg numbers correlate positively with survival in ALS, perhaps by altering the balance of harmful inflammation occurring in the brain and spinal cord. Patients with ALS recruited to MIROCALS will all take Riluzole for 3 months, then be randomised to receive additional ld IL-2 or placebo treatment for a further 18 months. A range of spinal fluid and blood molecular 'biomarkers' will be measured serially to correlate with clinical outcomes such as survival and functional status.

50 patients from MIROCALS will undergo MRI scans at baseline (on Riluzole only) and again 4-6 months after randomisation to treatment, along with 25 healthy age-matched controls for comparison. The novel MRI techniques to be used include Neurite Orientation Dispersion and Density Imaging (NODDI) which provide data on nerve cell architecture and density; quantitative magnetisation transfer (qMT) imaging which provides measures primarily on nerve cell insulation (myelin) content and composition; and resting state functional MRI (rsfMRI) to study the degree to which brain regions communicate at rest.

The principal brain regions of interest for analysis will be the brain surface controlling movement (primary motor cortices), the projection of these fibres into the spinal cord (corticospinal tracts) and a known resting state (sensorimotor) network, although whole brain analyses will be possible with the extensive imaging data acquired.

There is no active intervention or additional follow-up as the parent trial MIROCALS will do this over 18 months and share its data.

Intervention Type
Other

Primary outcome(s)
Current primary outcome measures as of 24/03/2017:
Quantitative magnetic resonance brain imaging data within the primary motor cortices, corticospinal tracts, corpus callosum and resting state sensorimotor network at baseline obtained by:
1. NODDI (including the Orientation Dispersion Index [ODI], Neurite Density Index [NDI], Isotropic Volume Fraction [ISO])
2. qMTi (including the f-value, kf value and T2f relaxation time)
3. rsfMRI (primarily the resting state sensorimotor network)

Previous primary outcome measures:
Quantitative multimodal magnetic resonance brain imaging data, obtained by:
1. NODDI (including the Orientation Dispersion Index [ODI], Neurite Density Index [NDI], Isotropic Volume Fraction [ISO])
2. qMTi (including the f-value, kf value and T2f relaxation time)
3. rsfMRI (using fluctuations in BOLD signal)
within the primary motor cortices, corticospinal tracts and resting state sensorimotor network at baseline

Key secondary outcome(s))
Current secondary outcome measures as of 24/03/2017:
Quantitative magnetic resonance brain imaging data within brain areas other than the primary motor cortices, corticospinal tracts, corpus callosum and resting state sensorimotor network at baseline obtained by:
1. NODDI (including the Orientation Dispersion Index [ODI], Neurite Density Index [NDI], Isotropic Volume Fraction [ISO])
2. qMTi (including the f-value, kf value and T2f relaxation time)
3. rsfMRI (other resting state networks such as the default mode network and frontoparietal network)

Previous secondary outcome measures:
Quantitative multimodal magnetic resonance brain imaging data, obtained by:
1. NODDI (including the Orientation Dispersion Index [ODI], Neurite Density Index [NDI], Isotropic Volume Fraction [ISO])
2. qMTi (including the f-value, kf value and T2f relaxation time)
3. rsfMRI (using fluctuations in BOLD signal)
within brain areas other than the primary motor cortices, corticospinal tracts and resting state sensorimotor network at baseline

Completion date
01/08/2019

Eligibility

Key inclusion criteria
Current inclusion criteria as of 24/03/2017:
For participants with MND/ALS enrolled in MIROCALS:
1. Patients of either sex
2. 18 to 75 years of age (inclusive)
3. Probable or laboratory probable, or definite ALS by El Escorial revised ALS diagnostic criteria (Brooks et al. 2000)
4. Disease duration ≤ 24 months
5. Vital capacity ≥ 80% of predicted
6. No prior or present Riluzole treatment
7. Patient able to provide signed informed consent
8. Patient able to lie flat in comfort for up to 50 minutes
9. No contraindication to MRI such as cardiac pacemaker
10. Able to journey to the University of Sussex campus in Falmer for the MRI scan

Previous inclusion criteria:
For participants with MND/ALS enrolled in MIROCALS:
1. Patients of either sex
2. 18 to 75 years of age (inclusive)
3. Probable or laboratory probable, or definite ALS by El Escorial revised ALS diagnostic criteria (Brooks et al. 2000)
4. Disease duration ≤ 24 months
5. Vital capacity ≥ 80% of predicted
6. No prior or present Riluzole treatment
7. Patient able to provide signed informed consent
8. Patient able to lie flat in comfort for up to 50 minutes

9. No contraindication to MRI such as cardiac pacemaker
10. Able to journey to the University of Sussex campus in Falmer for the MRI scan

For healthy age-matched control subjects:
1. Patient able to provide signed informed consent
2. Patient able to lie flat in comfort for up to 50 minutes
3. No contraindication to MRI such as cardiac pacemaker
4. Able to journey to the University of Sussex campus in Falmer for the MRI scan
5. No diagnosis of neurodegenerative or neurological disease

Participant type(s)
Mixed

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Other causes of neuromuscular weakness
2. Presence of other neurodegenerative diseases
3. Significant cognitive impairment, clinical dementia or psychiatric illness
4. Severe cardiac or pulmonary disease
5. Other diseases precluding functional assessments
6. Contraindication for lumbar puncture
7. Other life-threatening diseases
8. Documented auto-immune disorders except asymptomatic Hashimoto thyroiditis
9. Women of child-bearing age without contraception or pregnant or breastfeeding
10. Any clinically significant laboratory abnormality
11. Other concurrent investigational medications
12. Unable to take Riluzole
13. Patient unable to lie flat in comfort for up to 50 minutes for scan
14. Contraindication to MRI such as cardiac pacemaker
15. Patient unable to provide informed consent

Date of first enrolment
19/04/2017

Date of final enrolment
01/02/2019

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Princess Royal Hospital
Brighton and Sussex University Hospitals NHS Trust
United Kingdom
RH16 4EX

Study participating centre
Royal Sussex County Hospital
Brighton and Sussex University Hospitals NHS Trust
United Kingdom
BN2 5BE

Study participating centre
King's College Hospital
King's College Hospital NHS Foundation Trust
United Kingdom
SE5 9RS

Study participating centre
The National Hospital for Neurology and Neurosurgery
University College London Hospitals NHS Foundation Trust
United Kingdom
WC1N 3BG

Study participating centre
The Royal London Hospital
United Kingdom
E1 1BB

Study participating centre
Sheffield Royal Hallamshire Hospital
Sheffield Teaching Hospitals NHS Foundation Trust
United Kingdom
S10 2JF

Sponsor information

Organisation
CHU de Nimes

ROR
https://ror.org/0275ye937

Funder(s)

Funder type
University/education

Funder Name
University of Sussex

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
Universities (academic only)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The raw quantitative MRI imaging data will be stored anonymously and confidentially on the restricted-access university DICOM server for at least 10 years available to all members of the ANNALS-QuiCT research team. All individuals undergoing any scan at the CISC are assigned a unique code and their personal details stored securely in a locked facility at the CISC, separately from their scans. Only the ANNALS-QuiCT Project Site File will contain all identifiable participant data, forms and communications with participants for the duration of the study and be stored securely in the Research Centre. Computerised spreadsheets will be used to perform statistical analyses on anonymised data stored against codes and will be stored confidentially within a password protected university shared drive. Standards for metadata will comply with the University of Sussex Research Data Management Policy and participants will be consented to

these data storage practices. The project Chief Investigator will retain access for further analyses as appropriate. A University of Sussex repository (currently a subfolder on Sussex Research Online) will be used to archive the data, where needed.

IPD sharing plan summary

Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes