ISRCTN17945917 https://doi.org/10.1186/ISRCTN17945917

Investigating the role of miglustat in the management of a patient with Tangier Disease

Submission date
07/05/2021

Recruitment status
No longer recruiting

Registration date
07/06/2021

Overall study status
Completed

Last Edited
01/07/2021

Condition category
Nutritional, Metabolic, Endocrine

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

Plain English summary of protocol

Background and study aims
The study aims to determine if miglustat is an effective treatment for Tangier disease, in one patient. Tangier disease is a very rare inherited condition which interferes with how the body uses cholesterol. It leads to fat deposition in the arteries, tonsils, heart, and nerves. It can cause heart disease and can cause the nerves to stop working properly leading to clumsiness and loss of strength. It can lead to patients being unable to walk.

Until recently the only way to manage Tangier disease has been a low-fat diet, but this is not a cure, and patients often still develop disability. Previously, a patient with nerve damage thought to be due to another rare disease (Niemann-Pick type C) was given the treatment for the disease, a drug called miglustat. She actually had Tangier disease and had been misdiagnosed. She improved over several months, but when the misdiagnosis was recognised the treatment was stopped and over the next 6 months she deteriorated again. Her doctors then restarted miglustat, and she improved. This makes us think that miglustat may be useful in treating nerve damage in Tangier disease.

There is a patient in England who could benefit from miglustat. NHS England is willing to pay for this expensive drug but wants evidence that it works for this patient before they agree to provide it in the long term. The patient will alternately take miglustat, then no drug, for 6 months at a time, over 2 years.

We will assess how well their nerves are working on and off the drug, and other measures including quality of life and activities of daily living. We think we know how this treatment might work and will take blood samples during the study to see if our idea is right.

Who can participate?
There is a single participant study, where an adult participant with a diagnosis of Tangier Disease has already been identified and is known to the investigators.

What does the study involve?
The participant will complete four 6-month blocks where they will alternate between taking miglustat and not taking miglustat, alongside their usual care.

During the study, the participant will continue to go to their usual Tangier disease clinic every 6 months. At this visit, their doctor will complete a physical examination and take three blood samples and a urine sample as usual. These are used to measure their full blood count (the types and numbers of cells in the blood), lipids (the levels of different types of cholesterol in the blood), urea (a substance in their urine), and electrolytes (minerals found in the blood). The participant's doctor will also take some extra blood samples. These will be used to look at several different biomarkers (indicators of processes that happen in the body).

The participant will also complete two physiotherapist assessments every 2 months:
1. The 9-hole peg test, where the participant will be asked to place 9 pegs into a board, and then remove them as quickly as they can.
2. The hand grip and 3-point pinch tests where the participant will be asked to grip a device as hard as they can. This will be done using their whole hand, and by pinching between their thumb and their index and middle fingers.

The participant will complete two additional physiotherapist assessments every 6 months:
1. The 6-minute walk test where the participant will be asked to walk for 6 min, and the distance they have walked will be measured.
2. The 10 m walk test where the participant will be timed whilst they walk 10 m.

The participant will also be asked to complete a nerve conduction study every six months, where small pulses are applied to their skin to stimulate the nerve below. Finally, the participant will be asked to keep a food diary (where they record everything they eat and drink) for one week every 6 months.

What are the possible benefits and risks of participating?
There may not be any specific treatment benefits from taking miglustat. This study is being done as we don't know if miglustat is an effective treatment for Tangier disease. If miglustat does prove to be an effective treatment NHS England may continue to fund this medication for the participant. However, this depends on the study result, which we do not know yet.

The study treatment may not lead to an improvement in symptoms. Because Tangier disease is a progressive condition (it typically gets worse over time), symptoms may continue to get worse whilst taking miglustat. Miglustat may also cause unwanted side effects. The most common of these (very common side effects - these may affect more than 1 in 10 people) are diarrhoea, flatulence (wind), abdominal (stomach) pain, weight loss and decreased appetite. We do not know the effect of the drug on pregnancy, so the participant is asked to avoid becoming pregnant/fathering a child during the study.

If miglustat is effective, the participant may also experience periods of their symptoms improving whilst they are taking the treatment, and getting worse when they are not, which could be difficult to deal with.

The participant will be regularly monitored for any potential side effects. They will also be able to contact the research team, and independent emotional support throughout the study.

Where is the study run from?
Organised by the Southampton Clinical Trials Unit (UK) and sponsored by University Hospitals Birmingham NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
From December 2020 to April 2023

Who is funding the study?
The National Institute for Health Research (UK). The trial drug (miglustat) is being funded by NHS England (UK).

Who is the main contact?
Dr Tarekegn Hiwot
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

2020-005505-13

IRAS number
291868

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 48401, IRAS 291868

Study information

Scientific Title
Investigating the role of miglustat in the management of a patient with Tangier Disease: a single case experiment

Acronym
MUSTANG

Study objectives
Administration of miglustat in doses of up to 600 mg a day as tolerated will improve physical performance and quality of life in this patient.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 24/02/2021, North East - Newcastle & North Tyneside 2 Research Ethics Committee (NHS BT Blood Donor Centre, Holland Drive, Newcastle upon Tyne, Tyne and Wear, NE2 4NQ; +44 (0)207 1048091; newcastlenorthtyneside2.rec@hra.nhs.uk), ref: 21/NE/0048

Study design
Non-randomized interventional single case study

Primary study design
Interventional

Secondary study design
Single case study

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact email mustang@soton.ac.uk to request a participant information sheet.

Health condition(s) or problem(s) studied
Tangier disease

Interventions
This is a n-of-1 trial of ABAB design. This means that there will only be one participant who will receive alternating periods of treatment with miglustat plus usual care, and usual care only (on /off treatment conditions). Each treatment period is 6 months long, with the study lasting 2 years in total. During on-treatment periods the participant will take miglustat by mouth up to three times per day. The first treatment period will be an 'on treatment' condition.

The study design and methodology were chosen as Tangier Disease is very rare, there is only one participant in the UK who might benefit from treatment with miglustat. The use of an ABAB design means the study will be able to detect differences between ‘on’ and ‘off’ treatment periods in the primary outcomes in a single participant.

The single participant is known to the Co-CI (Dr Hiwot). The trial has been designed around their capabilities, including their perceived capacity and willingness for the outcome measures and how often they can attend review appointments.
The participant will be sent the PIS prior to attending their regular outpatient clinic. Written informed consent will be taken at the clinic, with the participant being given an opportunity to ask questions beforehand. The participant has also discussed the study with Co-CI Dr Hiwot during the study design process.

After consent has been given, the participant’s usual clinic will be completed, including physical examination and samples being taken to measure Full Blood Count (FBC), lipids, urea, and electrolytes. In addition to this, samples will be taken to complete a biomarker assessment, which is a study specific procedure (this would not be done as part of the participant’s usual care).

The participant will then complete primary and secondary baseline assessments with a physiotherapist. The primary assessments consist of:
1. A 9-hole peg test where the participant is asked to place 9 pegs into a board, and then remove them as quickly as they can. 2. Hand grip and 3 point pinch test, where the participant is asked to grip a device as hard as they can – firstly using their whole hand, and then by pinching between their thumb and index plus middle fingers.

The secondary assessments consist of:
1. A 6-minute walk talk where the participant is asked to walk for 6 min, and the distance they walk will be measured.
2. A 10-metre walk test where the time taken for the participant to walk 10 m is measured.

The participant will complete three baseline questionnaires:
1. EQ-5D-5L, a measure of health-related quality of life
2. Overall Neuropathy Limitations Scale, a measure of activities of daily living in relation to peripheral neuropathy (damage to nerve's in the body's extremities)
3. Rasch-build Overall Disability Scale, a measure of activities of daily living

The participant will be instructed how to complete a food diary. They will be asked to fill this in for one week every 6 months. This will be done in the week prior to their usual clinic visit, in month 6 of each intervention condition (i.e. either on/off treatment period).

The participant will also complete a baseline nerve function test (a test of how quickly a signal travels along nerves) at the Queen Elizabeth Hospital Birmingham.

The participant will then start taking miglustat as described above. Throughout the study, during both on/off treatment conditions the following measurements will be made:
1. Questionnaires and primary physiotherapist assessments every 2 months
2. Regular clinic visits, with additional biomarker assessment, will be completed every 6 months
3. Secondary physiotherapist assessments and nerve conduction study will be completed every 6 months

If the study is impacted by COVID-19 restrictions then the following adjustments will be made:
1. Questionnaires will be posted to the patient and administered via phone, or video call, with the participant's permission
2. Equipment (hand grip dynamometer and 9-hole peg test) for primary physiotherapist assessments will be posted to the patient and the tests will be administered via phone, or video call, with the participant's permission
3. Regular clinic visits (including biomarker assessment) will go ahead as usual, according to the hospital's COVID protocols
4. Nerve conduction study will go ahead as usual, according to the hospital's COVID protocols
5. Secondary physiotherapist assessment tests cannot be done remotely. If the patient is unable to attend the test in person, these will be missed for that treatment condition, with the reason for this being recorded.

The patient is currently deteriorating, so the trial will start as soon as relevant approvals are in place. The trial will last for 24 months.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Miglustat

Primary outcome measure
1. Fine motor control and finger dexterity measured by the time taken to complete the 9-hole peg test at baseline, 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24 months
2. Hand strength (grip strength and 3-point pinch strength) measured by force produced on the handgrip strength test and 3-point pinch strength test at baseline, 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24 months

Secondary outcome measures
1. Aerobic capacity and endurance measured by distance walked in the 6-minute walk test at baseline, 6, 12, 18, and 24 months
2. Gait, ambulation, and leg strength measured by time taken for the 10-metre walk test at baseline, 6, 12, 18, and 24 months
3. Quality of life is measured using the EuroQol 5-dimension 5-level (EQ-5D-5L) questionnaire at baseline, 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24 months
4. Activities of daily living are measured using the Overall Neuropathy Limitation Scale (ONLS) and the Racsh-built Overall Disability Scale (R-ODS) for immune-mediated peripheral

neuropathies questionnaires at baseline, 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24 months
5. Adverse events recorded using an adverse event form and are recorded throughout the trial
6. Nerve conduction measured using a nerve conduction study at baseline, 6, 12, 18, and 24 months
7. Clinical condition assessed using regular clinical assessment including physical examination, full blood count, measurement of lipids, urea, and electrolytes at baseline, 6, 12, 18, and 24 months
8. Mechanistic evaluation (investigating the potential mechanisms by which Miglustat does, or does not, have an effect) conducted by measuring biomarkers (relative lysosomal volume in circulating B cells; lipid analysis of circulating B cells; oxysterols; lyso-sm-509; lyso-sphingomyelin and bile acid derivatives) at baseline, 6, 12, 18, and 24 months

Overall study start date
01/12/2020

Completion date
28/04/2023

Eligibility

Key inclusion criteria
This is an n-of-1 study, where the potential participant has already been identified, and is known to the investigators there are limited inclusion and exclusion criteria:
1. Diagnosis of Tangier Disease
2. Aged ≥18 years
3. Willing and able to provide informed consent.
4. Agrees to use effective contraception throughout the study to avoid fathering a child

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Male

Target number of participants
Planned Sample Size: 1; UK Sample Size: 1

Total final enrolment
1

Key exclusion criteria
Severe renal impairment

Date of first enrolment

27/04/2021

Date of final enrolment
27/04/2021

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
University Hospitals Birmingham NHS Foundation Trust
Queen Elizabeth Hospital
Mindelsohn Way
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United Kingdom
B15 2GW

Sponsor information

Organisation
University Hospitals Birmingham NHS Foundation Trust

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Sponsor type
Hospital/treatment centre

Website
http://www.uhb.nhs.uk/

ROR
https://ror.org/014ja3n03

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Trial analysis and report writing will last up to 3 months, with the report being submitted to NHS England at the end of this period. Planned publication in a peer-reviewed journal.

Intention to publish date
28/04/2024

Individual participant data (IPD) sharing plan
Anonymous data will be available for request from three months after publication of an article, to researchers who provide a completed Data Sharing request form that describes a methodologically sound proposal, for the purpose of the approved proposal and if appropriate a signed Data Sharing Agreement. Data will be shared once all parties have signed relevant data sharing documentation. Researchers interested in our data are asked to complete the Request for Data Sharing form (CTU/FORM/5219) (template located on the SCTU web site, www. southampton.ac.uk/ctu) to provide a brief research proposal on how they wish to use the data. It will include; the objectives, what data are requested, timelines for use, intellectual property and publication rights, data release definition in the contract and participant informed consent etc. If considered necessary, a Data Sharing Agreement from Sponsor may be required.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No