A comparative phase2 study assessing the efficacy of triheptanoin, an anaplerotic therapy in Huntington's Disease (HD)

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The primary objective of TRIHEP 3 is to evaluate the efficacy of triheptanoin in (i) increasing the short term energy response in the metabolic profile of the brain of early affected HD patients, as captured by 31P-MRS, and (ii) slowing atrophy in...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Neurological disorders congenital
Study type	Interventional

Summary

ID

NL-OMON43815

Source
ToetsingOnline

Brief title
TRIHEP 3 in HD

Condition

- Neurological disorders congenital
- Movement disorders (incl parkinsonism)

Synonym
Huntington's Disease, neurodegenerative movement disorder

Research involving
Human

Sponsors and support

Primary sponsor: The French National Institute of Health and Medical Research (Inserm)
Source(s) of monetary or material Support: Inserm

Intervention

Keyword: Anaplerotic, Huntington's disease, Triheptanoin

Outcome measures

Primary outcome

a. An increase in the index of brain energy restoration * as defined by the difference between Pi/PCr ratio during visual stimulation and the mean of Pi/PCr ratio during rest and recovery * using P-MRS after 3 months of treatment.

b. A decrease in the rate of caudate atrophy, using volumetric MRI, after 6 months of treatment with triheptanoin in early affected HD patients.

Secondary outcome

Sustained restoration of brain energy metabolism using P-MRS after 6 months and 1 year of treatment

Decrease in the rate of caudate atrophy, using volumetric MRI, after 1 year of treatment with triheptanoin in early affected HD patients.

Improved diffusivity and/or fiber integrity, using DWI, after 6 months and 1 year of treatment.

The benefit of triheptanoin on motor function will be evaluated by a decrease in the progression of the UHDRS, the HD clinical reference scale with a motor score of up to 124 and of the TFC (Total Functional Capacity), a scale of patient autonomy, over 6 months and 1 year of treatment.

The benefit of triheptanoin on cognitive function will be evaluated every 6

months using a neuropsychological battery including the SDMT (Symbol Digit Modalities Test), a test of visuomotor coordination, the Stroop test, a test evaluating concentration and capacity for inhibition, the Digit-Span, a test evaluating attention and working memory, and the Trail Making Test to evaluate mental flexibility.

The effect of triheptanoin on psychiatric symptoms will be evaluated every 3 months with the PBA-S, an evaluation of problem behaviors associated with HD.

To investigate the effect of triheptanoin on quality of life short video's that will be recorded at the end of the randomized phase and a questionnaire will be used (SF-36).

Safety of triheptanoin will be evaluated based on review of adverse events and changes in clinical labs and physical examination/vital signs.

Long-term tolerance will be confirmed by clinical exam at study visits and by patient report during phone calls and home visits.

Changes in brain energy profiles will be correlated with volumetric measures and clinical rating scale scores.

Study description

Background summary

Huntington*s disease (HD) is an autosomal dominant disease characterized by movement disorders (chorea), behavioral, and neuropsychiatric disturbances. The clinical features of HD usually emerge in adult life and there is currently no curative treatment. The only existing treatment approved in HD is Tetrabenazine which treats irregular movements known as chorea, one of the major symptoms of HD. No treatment has yet been proven to slow, delay, or correct the course of the disease. Longitudinal imaging studies showed that caudate atrophy is the earliest change identified to date in the disease process. It has been shown to

be a more reliable indicator of disease progression than any existing clinical measures (Tabrizi, 2013). Other studies showed that energy deficit plays a critical role in the pathogenesis of HD. Specifically, weight loss was associated with a plasmatic decrease in branched chain amino acids in premanifest individuals on a high caloric diet (Mochel, 2007) suggesting the activation of compensatory mechanisms to provide energy substrates to the Krebs cycle. As a strategy to improve energy metabolism in HD, the following studies were carried out:
TRIHEP 1 demonstrated the safety and short-term metabolic correction in the muscle of the use of triheptanoin, an anaplerotic compound providing substrates to the Krebs cycle (Mochel, 2010). Using 31-Phosphorus Magnetic Resonance Spectroscopy (31P-MRS), PROMH 1 identified the inorganic phosphate/phosphocreatine (Pi/PCr) ratio as an outcome measure of brain metabolic dysfunction in HD patients (Mochel, 2012).
PROMH 2 confirmed the existence of an abnormal energy profile in HD patients, i.e. abnormal Pi/PCr ratio during brain activation, stable over time (Adanyeguh, 2015).
TRIHEP 2 tested the benefit of triheptanoin on the 31P-MRS metabolic profile of the brain and compliance. After one month of treatment, triheptanoin restored a normal Pi/PCr ratio in HD patients during brain activation (Adanyeguh, 2015).
TRIHEP 3 is a multi-centre (Paris and Leiden) randomized, double-blind, controlled study recruiting 100 early HD patients. Patients will receive either triheptanoin or a placebo for 6 months followed by a 6 month open-label phase with triheptanoin. The expected efficacy of triheptanoin will be measured by the caudate volume, brain energy metabolism using P-MRS, and clinical outcome measures

An extension period of 1 year may be proposed to patients who wish to pursue triheptanoin based on their perception of a possible clinical benefit.

Study objective

The primary objective of TRIHEP 3 is to evaluate the efficacy of triheptanoin in (i) increasing the short term energy response in the metabolic profile of the brain of early affected HD patients, as captured by 31P-MRS, and (ii) slowing atrophy in the caudate of early affected HD patients as measured with volumetric magnetic resonance imaging.

The secondary objectives are:
- Sustained restoration of brain energy metabolism after 6 months and 1 year of treatment.
- Decrease in rate of caudate atrophy after 1 year of treatment.
- To assess the clinical benefit of triheptanoin on motor function in HD patients using scores on the Unified Huntington*s Disease Rating Scale (UHDRS) and Total Functional Capacity (TFC).
- To assess the clinical benefit of triheptanoin on cognitive function and psychiatric symptoms in HD patients using scores on the neuropsychological

battery and the PBA-S.
- To investigate the effect of triheptanoin on quality of life short video's that will be recorded at the end of the randomized phase and a questionnaire will be used (SF-36).
- To look for correlations between neuroimaging volumetric parameters, brain energy profiles and clinical scores, before and after treatment.
- Safety of triheptanoin will be evaluated based on review of adverse events and changes in clinical labs and physical examination/vital signs.
- Long-term tolerance will be confirmed by clinical exam at study visits and by patient report during phone calls and home visits.
- Changes in brain energy profiles will be correlated with volumetric measures and clinical rating scale scores.

Study design

TRIHEP3 is a phase 2, multicenter double-blind, randomized, controlled two-armed study evaluating the efficacy of 1g/kg of body weight triheptanoin per day versus a placebo for a six month treatment period, followed by a 6 month open-labelled period with all patients treated with triheptanoin. An extension period of 1 year may be proposed to patients who wish to pursue triheptanoin based on their perception of a possible clinical benefit. Patiens who are willing to continue with the triheptanoin oil have to sign a new informed consent form.

Intervention

Treatment with triheptanoin or placebo (1g/kg), intake of triheptanoin/placebo 4 times a day (added to a meal) during the first 6 months. Followed by treatment with triheptanoin during the next 6 months.
The extension phase is a continuation of the open label phase with treatment of triheptanoin for the duration of 12 months.

Study burden and risks

Triheptanoin has been well tolerated with no significant safety issues. The most commonly reported adverse effects are gastro-intestinal distress and excessive weight gain at high doses.

Burden:
6 visits during 1 year at the Leiden University Medical Centre (LUMC). The screening visit last approximately 2 hours and all other visits lasts approximately half a day. Between the hospital visits a nurse will visit the subject at home 8 times. Furthermore, there will be regularly telephone contacts by the dietitian and/or other trial team members.

The following procedures will take place during the trial:

Blood samples (5x)
Urine samples (13x)
Pregnancy test (6x)
Dietary Consultation (6x)
MRI (4x)
Medical and neurological exam (5x)
Questionnaires and neuropsychological tests (3x)
Psychiatric evaluation (5x)

After the first 1-year treatment period an extension phase will be proposed to voluntary patients who wish to pursue triheptanoin based on their perception of a possible clinical benefit.
The following procedures will take place during the extension phase:
Blood samples (3x)
Urine samples (3x)
Pregnancy test, if applicable (3x)
Dietary Consultation (3x)
MRI (1x)
Medical and neurological exam (3x)
Questionnaires and neuropsychological tests (1x)
Psychiatric evaluation (1x)

Contacts

Public
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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- positive genetic test with CAG repeat length * 39 in HTT gene
- at least 18 years of age
- signature of informed consent
- UHDRS score between 5 and 40
- Ability to undergo MRI scanning

Exclusion criteria

- hypersensitivity to triheptanoin or to one of its excipients
- additional psychiatric or neurological conditions
- severe head injury
- farticipation in another therapeutical trial (3 months exclusion period)
- for women of childbearing age, the absence of two forms of effective contraception (with the exception of those who are abstinent)
- for men, the absence of an effective form of contraception (e.g. a condom) throughout the study period
- pregnancy or breastfeeding
- pnability to understand information about the protocol
- persons deprived of their liberty by judicial or unable to consent
- adult subject under legal protection or unable to consent
- treatment with tetrabenazine, sodium valporate, and pancreatic inhibitors

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial

Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-12-2015
Enrollment:	50
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	triheptanoin
Generic name:	triheptanoin

Ethics review

Approved WMO Date:	07-08-2015
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	11-12-2015
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	09-02-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	06-12-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	01-02-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	13-03-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	23-11-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	06-11-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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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
EudraCT	EUCTR2014-005112-42-NL
CCMO	NL53528.058.15