Thyroid hormone analog therapy of patients with severe psychomotor retardation caused by mutations in the MCT8 thyroid hormone transporter: The Triac Trial.

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1. Normalization of the abnormal serum TH parameters and thereby improving the clinical condition of the AHDS patients2. Observation of changes in cognitive and motor function.

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

Summary

ID

NL-OMON44458

Source
ToetsingOnline

Brief title
Triac Trial in MCT8 patients

Condition

- Endocrine disorders congenital
- Thyroid gland disorders
- Congenital and peripartum neurological conditions

Synonym
Allan-Herndon-Dudley Syndrome, MCT8 patient

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: ZonMw

Intervention

Keyword: Allan-herndon-Dudley Syndrome, MCT8, Thyroid hormone analog, Triac

Outcome measures

Primary outcome

1) Serum TSH, T4, vrij T4, T3, rT3 and Triac levels

Secondary outcome

1) Body weight, blood pressure and heart rate

2) Serum levels of markers that reflect peripheral thyroid hormone action: a.o.

serum steroid hormone binding globuline (SHBG) and lipids (liver), serum beta

Ctx and alkalisch phosphatase (bone) and serum kreatine kinase (muscle).

3) Motor function, using the Gross Motor Function Measure

4) Cognitive function using the Bayley Scales of Infant Development III or

Wechsler Preschool and Primary Scale of Intelligence II

5) Adaptive behavior according to Vineland adaptive behavior

scale

6) Basal Metabolic Rate using the Doubly labeled Water method

7) The frequency and nature of adverse events

Study description

Background summary

This therapeutic trial will be conducted in patients with the

Allan-Herndon-Dudly Syndrome (AHDS). AHDS is caused by mutations in MCT8. MCT8 is a thyroid hormone (TH) transporter protein, which is crucial for TH transport from the blood into different tissues. Loss of functional MCT8 results in strong decrease in intracellular TH levels (hypothyroidism) in tissues that depend on MCT8 for TH uptake. Local hypothyroidism in the brain of AHDS patients results in delayed neuronal growth and maturation. Consequently, AHDS patients present with severe psychomotor retardation.

In addition, AHDS patients have characteristic abnormalities in TH serum parameters: high T3, low T4 and normal TSH. The high T3 levels result in local hyperthyroidism in tissues that do not depend on MCT8 for TH uptake. This results in low body weight, muscle atrophy and an increased basal metabolism.

Currently no adequate therapy for these patients is available. A T3-analog that does not require MCT8 for its cellular uptake could restore part of the clinical phenotype. Several in vitro and animal studies have shown that the T3 analog Triac has a great potential.

Triac treatment could restore the abnormal TH serum parameters and Triac could replace the function of T3 in tissues that depend on MCT8 for TH uptake. This will result in 1) reduction of the toxic effects of the high T3 serum values leading to an increase in body weight and muscle mass and 2) restoration of adequate thyromimetic effects in tissues that depend on MCT8 for TH uptake which could have beneficial effects on the neurological phenotype.

Study objective

1. Normalization of the abnormal serum TH parameters and thereby improving the clinical condition of the AHDS patients
2. Observation of changes in cognitive and motor function.

Study design

Prospective interventional cohort study.

All included patients will receive the study medicine Triac. There will not be randomization or blinding. The daily Triac dose will be titrated individually based on serum thyroid hormone levels.

Intervention

Oral tablets of Triac, in 2-5 daily doses, during a study period of 12 months.

Study burden and risks

The burden of participation will consist of 10 extra hospital visits. During

control visits a routine physical examination and vena punctures will be performed. In addition, during the baseline visit and at the end of the study an extensive neurocognitive, cardiac and metabolic evaluation will take place.

Most control visits will coincide with appointments for regular care and will therefore form a minimal burden for the patients. All study procedures, except for vena punctures, are non-invasive and have no physical or emotional risk for the patients. Vena punctures are minimally invasive and have only mild risks.

There is worldwide experience with the application of Triac treatment in patients with abnormal TH serum values, including children. Reported side-effects are mainly dose-related and consist of symptoms of hyperthyroidism. Overdosing will be prevented by close follow-up and evaluation of recruited patients and by applying individual dose titration. Side-effect are transient and will subside within 2 days after dose reduction.
Given the scope of this study, it has to be conducted in patients with AHDS.
The benefits of Triac treatment are listed in the background section.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

clinical relevant and genetically confirmed mutation in the MCT8 gene, leading to the AHDS phenotype

Exclusion criteria

- Major illness or recent major surgery (within 4 weeks) unrelated to AHDS
- Patients who are participating in ongoing RCTs of therapeutic interventions (including clinical trials of investigational medicinal products);
- Patients that have any major contra-indication for Triac treatment (severe cardiac decompensation (NYHA 4), coronary insufficiency, severe cardiac arrhytmias, Galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption)

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-10-2014

Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Téatrois
Generic name:	Tiratricol

Ethics review

Approved WMO Date:	20-05-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-06-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-12-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-01-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-09-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-03-2016

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-05-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2014-000178-20-NL
ClinicalTrials.gov	NCT02060474
CCMO	NL47771.078.14