A national randomized placebo-controlled double-blind multicenter trial of LT4/LT3 combination therapy in patients with autoimmune hypothyroidism.

Published: 29-04-2021
Last updated: 10-01-2025

This study has been transitioned to CTIS with ID 2024-513883-24-00 check the CTIS register for the current data. Primary Objective: To investigate the effects of LT4/LT3 combination therapy compared to LT4 monotherapy on tiredness in those patients...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Thyroid gland disorders
Study type	Interventional

Summary

ID

NL-OMON54941

Source
ToetsingOnline

Brief title
T3-4-Hypo trial

Condition

- Thyroid gland disorders

Synonym
hypothyroidism; slow-acting thyroid gland

Research involving

Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: ZonMw Projectnummer: 848043003,Ace Pharmaceuticals B.V. Zeewolde

Intervention

Keyword: Hypothyroidism, Persistant complaints, Quality of Life, Triiodothyronine

Outcome measures

Primary outcome

The primary outcome measure is:

Mean change from baseline to 52 weeks in the ThyPRO tiredness subscale scores.

In case it is confirmed that LT4/LT3 combination therapy reduces tiredness compared to LT4 treatment alone, we will simultaneously investigate whether effect sizes are higher in patients with genetic variation in the type 2 deiodinase (DIO2-rs225014) and effect sizes are higher in patients with genetic variation in the monocarboxylate transporter 10 (MCT10-rs17606253), ensuring control of the studywise type 1 error (of 5% two-sided) across these three main questions.

Secondary outcome

Secondary study outcome parameters:

1. Mean change from baseline to 52 weeks in the ThyPRO-39 composite scale scores.

2. Improvement from baseline to 52 weeks in the ThyPRO tiredness subscale

scores >= minimal important difference (=14.3).

3. Mean change from baseline to 52 weeks in the ThyPRO tiredness subscale scores in participants with a baseline score > 57 (= population mean, unpublished results; personal communication with Dr T Watt, developer of the ThyPRO questionnaire).

4. Mean change from baseline to 52 weeks in the ThyPRO tiredness subscale scores in participants with a normal-range TSH level at 52 weeks.

5. Determinants of the effects of LT4/LT3 combination therapy on tiredness.

6. The (determinants of the) effects of LT4/LT3 combination therapy compared to LT4 therapy alone on other thyroid related complaints and quality of life.

7. The (determinants of the) effects of LT4/LT3 combination therapy compared to LT4 therapy alone on cardiovascular, metabolic, and bone outcomes.

8. The (determinants of the) effects of LT4/LT3 combination therapy compared to LT4 therapy alone on neurocognitive function.

9. Economic evaluation including cost-effectiveness analysis comparing LT4/LT3 combination therapy and LT4 monotherapy.

10. Number of adverse events in the LT4/LT3 combination therapy compared to the LT4 monotherapy groups.

Study description

Background summary

An underactive thyroid gland leading to a deficiency of thyroid hormones (hypothyroidism) affects up to 10% of the general population. The thyroid gland produces the inactive hormone T4, and to a lesser extent the active hormone T3. Additional production of T3 from T4 takes place in peripheral tissues. Because

thyroid hormone plays an important role in the function of virtually all human tissues, hypothyroidism causes many complaints, such as fatigue and neurocognitive complaints. The standard treatment for hypothyroidism is levothyroxine (LT4), which only contains T4. In most patients with hypothyroidism, LT4 is an adequate treatment with which the symptoms disappear. However,10-15% of patients experience persisting complaints, the most important of which is tiredness, despite normalization of blood thyroid hormone levels. This can result in decreased quality of life, loss of work and decreased participation to society. Unfortunately, there is no solution to this problem yet. An explanation for the aforementioned permanent disabling complaints may be that therapy with LT4 alone does not mimic physiology. An option is therefore to add LT3 to LT4 (LT4 / LT3 combination therapy). Although thousands of patients are currently being treated with this in the Netherlands, it is unclear whether and which patients benefit from this treatment.

Study objective

This study has been transitioned to CTIS with ID 2024-513883-24-00 check the CTIS register for the current data.

Primary Objective:
To investigate the effects of LT4/LT3 combination therapy compared to LT4 monotherapy on tiredness in those patients with autoimmune hypothyroidism and persisting tiredness on LT4 monotherapy, after 1 year of treatment.

In case it is confirmed that LT4/LT3 combination therapy reduces tiredness compared to LT4 treatment alone, the primary objective includes investigating simultaneously whether effect sizes are higher in patients with genetic variation in the type 2 deiodinase (DIO2-rs225014) and effect sizes are higher in patients with genetic variation in the monocarboxylate transporter 10 (MCT10-rs17606253).

Secondary Objective(s):
1. To investigate other determinants of effects of LT4/LT3 combination therapy compared to LT4 therapy alone on tiredness.
2. To investigate the (determinants of the) effects of LT4/LT3 combination therapy compared to LT4 therapy alone on other thyroid related complaints and quality of life.
3. To explore the (determinants of the) effects of LT4/LT3 combination therapy compared to LT4 therapy alone on cardiovascular, metabolic, and bone outcomes.
4. To explore the (determinants of the) effects of LT4/LT3 combination therapy compared to LT4 therapy alone on neurocognitive function.
5. To perform an economic evaluation including cost-effectiveness analysis comparing LT4/LT3 combination therapy and LT4 monotherapy.
6. To compare the number of adverse events during LT4/LT3 combination therapy

vs LT4 therapy alone.

Study design

The study design is: A national multi center double blind randomized placebo controlled study.

Intervention

The study starts with a run-in period in which all subjects switch to a generic LT4 preparation in order to prevent heterogeneity and bias in the RCT. An ECG is performed at baseline. The run-in period stops when the TSH is normal on generic LT4 and the patient still suffers from tiredness. The RCT starts 2 months afterwards to also achieve a mental steady state condition. A maximum of two dose adjustments are possible during the run-in period. The duration of the run-in period can therefore vary from 4-8 months.
In the RCT, LT3 / LT4 combination therapy is given in a 1:16 ratio, corresponding to the physiological ratio of T3 and T4. The patients in the LT4 / placebo arm will receive a placebo in addition to the standard LT4 treatment, due to the double-blinded nature of the study. The duration of the RCT is 1 year.

During the RCT the following interventions will take place:
- Physical examination (pulse rate/ blood pressure, weight, waist circumference) at 6 visits.
- TSH is measured at each visit and additional blood is drawn at the start and at the end of the RCT (genetic, metabolic, bone markers and biobank).
- An ECG will be performed at the start and at the end of the study.
- Questionnaires will be completed at six visits (ThyPRO, EQ-5D-5L, iPCQ and iMCQ).
- DEXA scans and neurocognitve test will be performed in a subgroup of 200 patients at the start and at the end of the RCT .

Study burden and risks

The study includes 9-11 visits in 1.5 years, depending on the number of dose adjustments required in the run-in period, while the normal contact frequency is ~4-6 times per year. If the subject is referred to a trial center, the travel time may take longer. The subjects may be confronted with their illness when completing the questionnaires / neurocognitive tests. The blood drawings may hurt or cause bruising. A DEXA scan is performed in a subgroup of 200 patients at the start as well as at the end of the RCT. This is a scan with a very low radiation exposure, which requires the patient to lie still for 10-15 minutes. LT3 is a drug approved by the Dutch Medicines Evaluation Board authority. The side effects of LT3 are in most cases due to oversupplementation

and disappear after dose reduction.

Contacts

Public
Erasmus MC, Universitair Medisch Centrum Rotterdam

Dr. Molewaterplein 40
Rotterdam 3015GC
NL
Scientific
Erasmus MC, Universitair Medisch Centrum Rotterdam

Dr. Molewaterplein 40
Rotterdam 3015GC
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Patients with overt or subclinical hypothyroidism 18 years or older.
LT4 monotherapy for at least 6 months.
LT4 monotherapy dose of 75-225 microg, with at least a dose of 1.2 microg/kg.
TSH levels within the assay-specific reference ranges for at least 3 months.
Severe tiredness with a large negative impact on daily life for at least 6 months, with or without other persisting complaints. This is based on the patient's own experience, without judgment of the treating physician.

Sufficiently fluent in Dutch and able to read Dutch.

Exclusion criteria

Thyroid surgery Radioactive iodine treatment Use of thyroid interfering drugs (current/past use of amiodarone, immunotherapy, tyrosin kinase inhibitors, interferon or lithium and current use of oral or iv corticosteroids or dopamine) Current psychiatric disease treated at a "gespecialiseerde GGZ instelling" Clinical diagnosis of dementia Pregnancy, breastfeeding or wish to become pregnant within 2 years Current/past atrial fibrillation Functional or structural abnormal heart (e.g. cardiomyopathy or valve disease) Current conduction disorder on ECG (i.e. Prolonged QRS > 100 ms; or prolonged QTc; QTc women > 460 msec / men > 450 msec) Frequent ventricular extrasystole (=doublet, trigeminy, bigeminy or (non-sustained) ventricular tachycardia) in the past or on current ECG Recent acute coronary syndrome or unstable angina pectoris (< 4 weeks) Other obvious medical explanation for tiredness (e.g. end-stage renal disease, anemia, COPD stage IV, cancer, etc.) Other obvious major life event explanation for tiredness (e.g. mourning, loss of job)

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	19-10-2022
Enrollment:	600
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cytomel
Generic name:	Liothyronine - Triiodothyronine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Levothyroxine
Generic name:	Levothyroxine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	29-04-2021
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-10-2021
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-02-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-02-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-03-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	20-06-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-08-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-12-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-12-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-03-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-04-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-08-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-09-2024

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-10-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-10-2024
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

ID: 22866
Source: NTR
Title:

In other registers

Register	ID
EU-CTR	CTIS2024-513883-24-00
EudraCT	EUCTR2020-003214-12-NL
CCMO	NL74281.078.21
Other	NL9314 (Nederlands Trial Register)