A national randomized placebo-controlled double-blind multicenter trial of LT4/LT3 combination therapy in patients with autoimmune hypothyroidism: the T3-4-Hypo trial.

Gepubliceerd: 08-03-2021 Laatst bijgewerkt: 15-05-2024

Addition of liothyronine (LT4/LT3 combination therapy) in patients with persistent tiredness on LT4 monotherapy is effective in relieving tiredness.

Ethische beoordeling	Positief advies
Status	Werving nog niet gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON22866

Bron
NTR

Verkorte titel
T3-4-Hypo Trial

Aandoening

overt or subclinical hypothyroidism

Ondersteuning

Primaire sponsor: Erasmus Medical Center Rotterdam
Overige ondersteuning: ZonMw Project number 848043003

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

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.

Toelichting onderzoek

Achtergrond van het onderzoek

Rationale: Hypothyroidism is common, affecting 5% of the general population, for which levothyroxine (LT4) monotherapy is the standard treatment. Despite normalized serum thyroid hormone levels, 10-15% of LT4 treated patients have various persistent complaints, the most important of which is tiredness. This could be explained by the fact that physiological T4/T3 ratios cannot be reached with LT4 monotherapy, as in a healthy individual T3 is not only derived from T4/T3 conversion but is also directly produced by the thyroid itself. Studies have reported contradicting results as to whether addition of liothyronine (LT4/LT3 combination therapy) in patients with persistent tiredness on LT4 monotherapy is effective or not. Studies have suggested higher effectiveness in patients carrying genetic variation in the type 2 deiodinase (DIO2-rs225014) and monocarboxylate transporter 10 (MCT10-rs17606253) genes.
Objective: To investigate whether addition of liothyronine (LT4/LT3 combination therapy) in in patients with persistent tiredness on LT4 monotherapy is effective or not in relieving tiredness.
Study design: National randomized placebo-controlled double-blind multicenter trial.
Study population: Six hundred patients ≥ 18 years with autoimmune hypothyroidism who despite biochemical euthyroidism with LT4 monotherapy have persistent tiredness with a negative impact on daily life.
Intervention (if applicable): First, all participants are switched to the same generic LT4 preparation as there are seven LT4 preparations available in the Netherlands with different pharmacokinetic properties, which would otherwise introduce bias. Next, the intervention group is treated with once daily a LT4 tablet and twice daily a LT3 tablet with a LT4:LT3 ratio 16:1. The control group is treated with once daily a LT4 tablet and twice daily a placebo tablet. Treatment duration is 52 weeks.
Main study parameters/endpoints: The ThyPRO tiredness subscale scores at 52 weeks follow-up. 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 DIO2 (rs225014) and MCT10 (rs17606253), ensuring control of the study-wise type 1 error (of 5% two-sided) across these three main questions.

Doel van het onderzoek

Addition of liothyronine (LT4/LT3 combination therapy) in patients with persistent tiredness on LT4 monotherapy is effective in relieving tiredness.

Onderzoeksopzet

Primary outcome after 52 weeks of treatment

Onderzoeksproduct en/of interventie

First, all participants are switched to the same generic LT4 preparation as there are seven LT4 preparations available in the Netherlands with different pharmacokinetic properties, which would otherwise introduce bias. Next, the intervention group is treated with once daily a LT4 tablet and twice daily a LT3 tablet with a LT4:LT3 ratio 16:1. The control group is treated with once daily a LT4 tablet and twice daily a placebo tablet. Treatment duration is 52 weeks.

Contactpersonen

Publiek

Erasmus Medical Center
Marco Medici

+31 10 7040570

Wetenschappelijk

Erasmus Medical Center
Marco Medici

+31 10 7040570

Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

- Patients with overt or subclinical primary hypothyroidism aged 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.

*Thyroid peroxidase (TPO) and/or thyroglobulin (Tg) antibody positivity is not a requirement as these have frequently not been determined. Instead, we ensure that we only include patients with autoimmune hypothyroidism by excluding other causes of hypothyroidism (see exclusion criteria).

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

- Congenital hypothyroidism, hypothyroidism after (sub)acute thyroiditis, secondary (central) hypothyroidism.
- Thyroid surgery, radioactive iodine treatment, or head and/or neck radiotherapy.
- 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.
- Women of reproductive age not using adequate contraception, who are not sterilized and do not have a sterilized partner. Adequate contraceptives include the contraceptive pill, patch, injection, implant, intrauterine device or system, vaginal ring, diaphragm or cap, and condom.
- Functional or structural abnormal heart (e.g., cardiomyopathy or valve disease)
- Recent acute coronary syndrome or unstable angina pectoris (<4 weeks)
- Current/past atrial fibrillation
- Current conduction disorder on ECG (i.e, QRS>100 ms or prolonged QTc (women≥460 ms and men≥450 ms)).
- Frequent ventricular extrasystole (=doublet, trigeminy, bigeminy or (non-sustained) ventricular tachycardia) in the past or on current ECG.
- 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)

*Treatments of mild non-complex psychological/psychiatric complaints are done in the " basis GGZ", e.g. consisting of conversations with a psychologist or psychotherapist, or via internet (e-health). "Gespecialiseerde GGZ" encompasses treatments of more severe psychological/psychiatric complaints.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Parallel
Toewijzing:	Gerandomiseerd
Blindering:	Dubbelblind
Controle:	Placebo

Deelname

Nederland

Status:	Werving nog niet gestart
(Verwachte) startdatum:	15-06-2022
Aantal proefpersonen:	600
Type:	Verwachte startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nog niet bepaald

Ethische beoordeling

Positief advies

Datum:	08-03-2021
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

ID: 54941
Bron: ToetsingOnline
Titel:

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL9314
CCMO	NL74281.078.21
OMON	NL-OMON54941

Resultaten