TETRA-pilot: Testosterone in transgender women after vaginoplasty: a dose-finding and feasibility pilot study

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Endocrine disorders of gonadal function
Study type	Interventional

Summary

ID

NL-OMON51335

Source
ToetsingOnline

Brief title
TETRA-pilot

Condition

- Endocrine disorders of gonadal function

Synonym
gender-affirming hormone treatment, Hypogonadism

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,Kyowa Kirin Ltd

Intervention

Keyword: Dose-finding, Estradiol, Testosterone, Transgender

Outcome measures

Primary outcome

To establish dose-response relationship, the main study parameters are the testosterone levels at different daily dosages of 2.5 mg (1/4th pump), 3.3 mg (1/3rd pump) and 5 mg (1/2nd pump) at the short-term (minimum 2 weeks) and after two months of continuous use. When testosterone levels between 1.5 and 2.5 nmol/l have been reached, the participants will continue on that dose for two months in which testosterone levels are determined every month. At each visit, changes in symptoms of androgenism are assessed which include facial and bodily hair growth, alopecia, acne and application site symptoms.

Secondary outcome

Secondary endpoints include the evaluation of a clinical symptoms questionnaire to assess the expected effects of changes in serum testosterone concentrations. Finally, for participants who wish to participate in the elective part of the study, feasibility of measuring changes in vaginal pulse amplitude (VPA) will be assessed using photoplethysmography during different erotic stimuli.

Study description

Background summary

Transgender women have a female gender identity that does not match their assigned male sex at birth. In order to induce secondary female characteristics, transgender women may receive hormone therapy through estradiol and anti-androgen therapy. Subsequently, transgender women may choose

to undergo a vaginoplasty where the testicles are removed and a neovagina is created. After a vaginoplasty, testosterone levels are lower than those found in ovulating cisgender women (female sex assigned at birth, female gender identity), which may cause symptoms associated with hypogonadism such as fatigue, depressed mood, cognitive decline, reduced sexual desire and arousability. Low testosterone levels may also limit genital blood flow during subjective sexual arousal. In postmenopausal cisgender women with low testosterone levels and similar complaints, low-dose transdermal testosterone therapy is recommended and has no severe side-effects. However, no adequate testosterone formulation is available for use in women and dose-response relationships differ after short-term and longer term serum analysis. One pilot study in transgender women reported that low-dose testosterone supplementation had a positive effect on symptoms of low sexual desire, but the dose to reach physiological testosterone levels that are comparable to cisgender women, as well as the prevalence of sides effects, currently remain unknown.

Study objective

The primary objectives are to establish dose-response relationship for 2% transdermal testosterone (Tostran®) gel to achieve total testosterone serum concentrations between 1.5-2.5 nmol/l in transgender women after vaginoplasty and to assess side effects of androgenism at the different dosages. Secondary objectives are to assess the feasibility and applicability of a clinical symptoms questionnaire.
Finally, in a subgroup of participants who provide additional consent for an elective part of the study, we aim to assess the feasibility of vaginal pulse amplitude measurements using photoplethysmography.

Study design

This is a non-blinded pilot study with two phases: a step-wise dose-titration phase and a dose-continuation phase.

Intervention

During the study, participants will receive 2% transdermal testosterone gel (Tostran®) daily. During the dose-titration phase, participants will receive daily doses of 2% transdermal testosterone gel (Tostran®) at 2.5 mg (1/4th pump), optionally 3.3 mg (1/3rd pump) and optionally 5 mg (1/2nd pump) in a step-up scheme in three to four week intervals. Considering the bioavailability of 12% of Tostran®, this amounts to 300 ug/day for the first two weeks, 396 ug/day during the next four weeks and 600 ug/day during the final four weeks. When a total testosterone serum concentration between 1.5 and 2.5 nmol/l has been reached, no further dose-increase will take place and participants will enter the dose-continuation phase where they continue on the established daily

dose for two months.

Study burden and risks

The dose-titration phase will include maximum four one-hour visits to the clinic: at baseline and at two weeks for all participants and at six after baseline for participants whose receive a first dose-increase and at ten weeks after baseline for participants who receive a second dose-increase. When participants have a serum total testosterone level between 1.5-2.5 nmol/l, they will cease further dose-increase and remain on this dose for three months in which they will visit the clinic every month for clinical evaluation where side-effects are evaluated and blood is drawn. After signing informed consent, participants will be asked to fill out a questionnaire to assess baseline symptoms of adrogenism and clinical symptoms of hypogonadism. Afterwards, max 17.5 mL (4 tubes) blood will be drawn and weight, height, blood pressure and heart rate will be measured. During the following visits in the dose-escalation phase, blood will be drawn and side-effects of androgenism will be assessed. In the two month dose-continuation phase, participants will visit the clinic monthly and side-effects are assessed and blood is drawn. Additionally, at the final visit, the clinical symptoms questionnaire will be filled in. During the study, participants will continue their regular visits to the gender clinic if these have been scheduled and we aim to schedule these on the same day as a study visit. The risk associated with the investigational treatment are expected to be limited and reversible. The mildly increased levels of testosterone may cause slightly increased facial and body hair, slight weight increase and mild acne. The application of the gel may cause dryness of the skin at the application site. An uncommon side effect may be alopecia. A rarely reported side effect in cisgender women is deep venous thrombosis, but it is likely that this risk arises from the concurrent use of estrogens that transgender women are already using before the study. Studies show no increased risk of polycythemia and adverse lipid profiles when using transdermal application at these low concentrations(1). There is no risk of voice changes because the irreversible deepening of the voice associated with testosterone has already taken place in transgender women who underwent physiological puberty and initiated hormone therapy after 18 years of age. Available data suggest that short-term transdermal testosterone therapy does not impact breast cancer risk.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Start of gender affirming hormone therapy at or after 18 years of age
- Current use of estradiol therapy with good compliance for at least one year
- Underwent vaginoplasty
- Sufficient knowledge of the Dutch language
- BMI 18-30 kg/m2
- Testosterone levels <0.8 nmol/l measured since vaginoplasty
- To participant in optional vaginal pulse amplitude measurement: minimal self-reported vaginal depth of five centimeters

Exclusion criteria

- No regular follow-up visits at the clinic for gender dysphoria
- Previous use of testosterone therapy
- Current treatment for depression
- Severe familial dyslipidemia (e.g. Familial Hypercholesterolemia)
- Serum estradiol concentration lower than 150 pmol/l or higher than 700 pmol/L the VUmc reference range (150-700 pmol/L) at last visit prior to baseline.
- Mental health issues that prevent participation

- Hematocrit at last visit prior to baseline of >0.49 l/l
- Current use of anticoagulation treatment or corticosteroids
- Any of the following contraindications for the use of testosterone gel (Tostran®): Known, past or suspected breast cancer; Known or suspected estrogen-dependent malignant tumours (e.g genital tract carcinoma); Acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal (<2.5xULN); Porphyria; Cerebral hemorrhage; Known hypersensitivity to the active substances or to any of the excipients (Propylene glycol, Ethanol anhydrous, Isopropyl alcohol, Oleic acid, Carbomer 1382, Trolamine, Butylhydroxytoluene (E321), Hydrochloric acid (used for pH adjustment)); Interfering medication (SPC).

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):	26-10-2022
Enrollment:	10
Type:	Actual

Medical products/devices used

Generic name:	vaginal photoplethysmography
Registration:	No
Product type:	Medicine
Brand name:	Tostran 2% Gel
Generic name:	Testosterone
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	17-05-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-06-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-03-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2021-005344-30-NL
CCMO	NL79312.029.22