A GnRH Agonist IN pre-menopausal women STudy to treat severe Polycystic Liver Disease

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This study has been transitioned to CTIS with ID 2023-506637-30-00 check the CTIS register for the current data. The main objective of this study is to determine whether lowering estrogen and progesterone levels with leuprorelin decreases liver...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Hepatobiliary disorders congenital
Study type	Interventional

Summary

ID

NL-OMON50796

Source
ToetsingOnline

Brief title
AGAINST-PLD

Condition

- Hepatobiliary disorders congenital
- Hepatic and hepatobiliary disorders
- Renal disorders (excl nephropathies)

Synonym
Cystic livers, Polycystic liver disease

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen

Source(s) of monetary or material Support: ZonMW subsidie Goed Gebruik Geneesmiddelen;nr 10140261910001

Intervention

Keyword: Estrogen, GnRH agonist, Liver volume, Polycystic liver disease

Outcome measures

Primary outcome

The primary outcome is the livergrowth, in percent per year, calculated from BL till t=1.5 years, compared between the direct start groep (receiving leuproreline treatment in this period) and the delayed start group (serving as a control group).

Secondary outcome

1. Change in PLD-related complaints, measured by the score on the validate PLD-questionnaire, comparing the change in PLD-Q score in the first 1.5 years between the direct start group and the delayed start group. c

Exploratory outcomes:

- height adjusted liver volume, compared between the direct and delayed start groep after 1.5 years

- estrogen levels, compared at BL, 3 months after start treatment, 1.5 years, 21 months and 3 years

- acute effects of the treatment, using the MRI or CT scans 6 months after start of treatment

- safety and toleratability, incidence of (serious) adverse events,

bone-density measured using DEXA-scans, drop-out rate

- Quality of life, assessed by het SF-36 and BD-II

- menopause related complaints, assessed by the MENQOL-questionnaire

In patients with polycystic kidney disease

- growth rate of kidney volume in the first 1.5 years, compared between the direct start group and delayed start group

- growth rate of kidney volumes, compared within individuals, before start of treatment and during treatment

- acute effects of the treatment, using the MRI or CT scans 6 months after start of treatment

- change in renal function in the first 1.5 years between direct and delayed start group

Study description

Background summary

Polycystic liver disease (PLD) is a rare but severe disease, characterized by enlargement of the liver due to the growth of numerous cysts. Two autosomal dominant hereditary diseases are known to cause this phenotype: Autosomal Dominant Polycystic Liver disease (ADPLD) and Autosomal Dominant Polycystic Kidney Disease (ADPKD) the latter also causing cyst growth in the kidneys and renal function decline. Together, approximately 4 per 100.000 subjects in the general population suffer from PLD.

The large liver volume results in compression of stomach and bowels, and thus to early satiety, decreased food intake, weight loss and constipation. The high intra-abdominal pressure also leads to heart-burn, and umbilical and inguinal herniation. These medical problems often force affected patients to stop working. The large, protruding abdomen may also cause psychological problems, because of a distorted body image and confronting questions about being

pregnant. The median liver growth is 3.9% per year, but can be as high as 20% per year in some cases, resulting in liver volumes of up to 7.5 to 15 liters. The only available treatment at this time is a somatostatin analogue, such as lanreotide or octreotide, that is injected subcutaneously or intramuscular once monthly. This drugs slows the rate of liver growth in polycystic liver patients. However, especially in the patients with the fastest growth rates, which are mostly young women, the liver continues to grow fast. These patients have the risk of developing severe complaints, with reduced quality of life, and finally even a need of a liver transplantation. These patients will be the target group to be included in our study.

The last years, it has become clear that female hormones, including estrogen and progesterone, have a stimulating effect on cyst growth in polycystic liver disease. Estrogen receptors are present on cystic liver tissue but not on normal liver tissue, in vitro, administration of estrogen enhances proliferation and administration of estrogen blockers decreases proliferation. It was already known from epidemiological studies that estrogen, for example in oral contraceptives or hormone replacement therapy, promotes livergrowth in polycystic liver disease. Very recently, data was published that showed that liver growth, and sometimes even liver volumes, decreased after menopause.

The aforementioned recently published experimental and epidemiological data have led us to hypothesize that lowering estrogen and progesterone levels in women with severe PLD will ameliorate the disease process, by decreasing liver growth and its related complaints, improving quality of life, and ultimately preventing the need for liver transplantation. In this study, we will test this hypothesis using the GnRH analogue leuprorelin to stop the production of estrogens and progesterone.

Study objective

This study has been transitioned to CTIS with ID 2023-506637-30-00 check the CTIS register for the current data.

The main objective of this study is to determine whether lowering estrogen and progesterone levels with leuprorelin decreases liver growth rates in pre-menopausal women with severe PLD.
Secondary objectives are to assess in these women the effect of leuprorelin on PLD-related complaints, quality of life, tolerability and safety.

Study design

This is an investigator-driven, randomized, controlled open label trial with blinded endpoint assessment (PROBE). Patients will be screened for in- and exclusion criteria and counseled carefully about the treatment and possible side effects. If eligible and after having given consent, patients will be

randomized to direct or delayed start (18 months later) of leuprorelin treatment.

The randomization between direct and delayed start is important to distinguish if any observed effect on the rate of growth is due to the natural course of the disease while ageing, or due to the medical intervention (primary endpoint). Patient blinding is not possible, since leuprorelin will induce menopause. The trial is therefore open label. After 18 months, patients in the delayed start group will start with leuprorelin treatment. The addition of a delayed start group to the trial design has been introduced to replace the traditional placebo group. This design reflects the urgency felt by patients that we have consulted. Patients emphasized that, given the recent epidemiological evidence, they would not participate in a trial if there would be a chance to be in a control group, without treatment. Furthermore, this switch to treatment after 18 months enables a paired analysis of intra-individual change in rate of liver growth (comparing growth before and after start of treatment) in all patients. Finally, it will render additional tolerability data. The patients in the direct start group will not cross over to no-treatment because of two reasons: first these patients will experience menopause two times. Second, treatment in the first 1,5 year can have an unexpected prolonged carry-over effects, so it could be questioned whether these patients can serve as proper controls in the second phase.

At the end of study, but depending on the study site, patients will be allowed to continue study medication, until study results are available. Treatment will be stopped at age 55, since >= 95% of women will have reached natural menopause by then.

Intervention

At the start of the study, patients will be randomized between direct start of treatment, and delayed start (after 1.5 years). Leuprorelin is a GnRH analogue that stimulates the pituitary to produce LH and FSH. If used for a longer term, desensitization occurs and the pitutary will produce no LH and FSH anymore. In this way, a chemical menopause is induced, and the ovaries will not produce estrogen and/or progsterone anymore.
Since the drug causes side-effects similar to menopause (for example cessation of menopause), a blinded placebo controlled study design is not an option. We therefore choose for a PROBE design (i.e. prospective, randomized, open label, with blinded endpoint assessment).

Treatment is started as monthly subcutaneous injections of 3.75 mg for the first three months, and when tolerated, as three-monthly injections of 11.25 mg thereafter.

Study burden and risks

The study consists of 10 study visits in 3 years. During the study, 5 times and MRI or CT scan will be made and laboratory measurements and vital signs will be performed every visit.

The study treatment consists of (subcutaneous) injections, first monthly and after 3 months, if tolerated, 3-monthly injections. The patient can self-administer this injections to reduce the hospital visits.

Dependent on the study site, these study visits will replace part or most of the regulary visits to the outpatient clinic.

Leuprorelin could lead to short-term side effect such as hot flushes, palpitations, mood swings, vaginal dryness and other side effects related to low estrogen levels. On the longer term, treatment could lead to reduced bone density and a slightly enhanced cardiovascular risk.

All patients meeting the inclusioncriteria have a very severe form of polycystic liver disease, leading to pain, reduced intake, reduced mobility, and a decreased quality of life. For all patients participating in this trial, there are currently no other treatment options available than a liver transplantation, an invasive procedure bearing several short- and long-term risks. In a focusgroup with 8 patients meeting the inclusion criteria, we discussed wheter patient would we willing to try such a treatment or participate in this trial weighing the side-effects of treatment versus the prospects of their disease. All patients stated that they would be willing to participate in the trial.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Female patients with PLD - Age 18 to 45 years - Very large height adjusted liver volume for age: 18-30 yr >2.0 L/m; 30-35 yr >2.2 L/m, 35-40 yr > 2.5 L/m and >40 years >3.0 L/m - Confirmed ongoing liver growth - Since somatostatin analogues are proven efficacious therapy for PLD at this time it is required that patients use a somatostatin analogue and still have liver growth (as mentioned above) or the patient has a specific reason not to use this medication (e.g. patient used a somatostatin analogue in the past, but had to stop it due to inefficacy or because they did not tolerate it, or they have a contra-indication for using somatostatin analogues) - Availability of at least 1 historical MRI or CT scan made between 5 to 1 years before baseline visit

Exclusion criteria

- Post-menopausal status or (vasomotor) symptoms indicating upcoming menopause; - AMH measurement at screening < 0.3 - Active desire to have pregancy; - Contra-indications for leuproreline, such as history of cardiovascular disease, history of osteoporosis or osteoporosis at the dexa-scan at screening; - Liver transplantation expected in the next 1.5 years - Use of estrogen or progesterone containing medication

Study design

Design

Study phase: 2

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	29-12-2022
Enrollment:	36
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Lucrin
Generic name:	leuprorelin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	21-10-2021
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-10-2021
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-07-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	04-04-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-04-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-06-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-09-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-10-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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
EU-CTR	CTIS2023-506637-30-00
EudraCT	EUCTR2020-005949-16-NL

Register	ID
CCMO	NL76163.042.21