Ulipristal versus standard surgical treatment in symptomatic uterine fibroids

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This study has been transitioned to CTIS with ID 2024-512602-26-00 check the CTIS register for the current data. Evaluate the (cost-) effectiveness of ulipristal in comparison with standard surgical treatment for symptomatic uterine fibroids,...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Reproductive neoplasms female benign
Study type	Interventional

Summary

ID

NL-OMON52721

Source
ToetsingOnline

Brief title
MYOMEX-2

Condition

- Reproductive neoplasms female benign

Synonym
fibroids, myoma

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: ZonMw

Intervention

Keyword: Hysterectomy, Myomectomy, Ulipristal, Uterine fibroids

Outcome measures

Primary outcome

Outcomes with regard to patient:

1) Fibroid-specific quality-of-life, measured by the Uterine fibroid symptom-questionnaire (UFS-QOL) symptom severity score (SSS) outcome at 24 months after randomization

Outcomes with regards to costs (using internet medical consumption questionnaires; iMCQ):

1) Direct health care costs

2) Costs due to loss of productivity (absenteeism from work)

3) Patient costs (informal care, other care services paid for by patients themselves)

Secondary outcome

Secondary outcomes with regard to patient:

1) What is the effect of the intervention on quality of life parameters, such as pain, societal participation and sexual functioning?

2) What is the effect of the intervention on fibroid specific complaints such as volume reduction (UPA group); amount of menstrual bleeding (PBAC-score) and Hemoglobin level.

3) What is the re-intervention rate in both treatment groups and how many

patients choose for an intervention after treatment with UPA??

4) What is the effect on patient preference and satisfaction?

5) Which complications/side-effects occur?

6) What is the effect of UPA-usage on the blood results, regarding liver

function?

7) Which sub-groups benefit most within the study group (subgroup-analysis)

Study description

Background summary

Fibroids are the most common benign tumors in women of reproductive age, occurring in up to 80% of the population, with 20-50% of those requiring clinical intervention. Fibroids are therefore a major source of healthcare costs: in the Netherlands around 7500 hysterectomies are performed for this indication, with annual in-hospital costs of 30.000.000 euro*s. Up to now, fibroid surgery is the gold standard, but not always preferable. Although hysterectomy usually solves a lot of fibroid complaints, pregnancy is impossible and long term complications such as stress-urinary-incontinence (SUI) surgery can occur. Uterus-sparing surgeries are related to recurrence of the fibroids or scarring of the uterus, which could also influence fertility outcomes. For all three fibroid surgeries accounts that severe complications can occur in 1 out of 100 patients during and after surgery, such as haemorrhage, vesicoperitoneal fistula, ureteral injury, rectal perforation or fistula.

Ulipristal Acetate (UPA) was introduced in 2012 as a new treatment option for symptomatic uterine fibroids. UPA is a selective progesterone receptor modulator with effect on fibroid volume and fibroid related complaints. The effectiveness of UPA is evaluated in the PEARL trials. UPA was first evaluated as a pre-treatment before surgical treatment of uterine fibroids.
Pre-treatment consisted of a daily 5 mg tablet during a 3 months period prior to surgery leading to a median volume reduction of 36% (IQR 11-58%). Also bleeding complaints decreased dramatically, leading to amenorrhea in 79% of the patients and thereby offering a better pre-operative condition for patients.
Recently long-term treatment with UPA was evaluated in the PEARL III&IV trials. In total four (3 months) treatment courses were administered separated by treatment free intervals of 2 months. Quality of Life (QOL) scores were obtained using the Uterine Fibroid Symptoms questionnaire (UFS-QOL), a

validated QOL tool for fibroid symptoms that breaks down to a Symptom Severity Score (SSS) and a general QOL score. SSS (0-100) diminished from 50 to 16 points (70% improvement) and general QOL (0-100) improved form 57 to 84 (almost 50% improvement also). Volume reduction augmented during the courses up to 65% after the fourth course. Amenorrhea rates were 74%, 73%, and 70% in women who received treatment courses 2, 3, and 4, respectively.
UPA was launched as a revolutionary medication for fibroids, claiming to make invasive treatment unnecessary. UPA is however quite costly and has never been compared to other treatment modalities. Furthermore there is some concern about the long-term effects on the endometrium. Very recently (November 2017), the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicine Agency (EMA), started a procedure to investigate ulipristal, due to a possible relation between the medicine and a very rare form of liver injury: Drug Induced Liver Injury (DILI). The PRAC concluded that a possible relation between ulipristal and DILI is unsure, but can't be excluded or proven. Therefore they recommend risk-minimization measures to trace possible liver injury in a very early stage and to ensure that this injury is reversibel. These risk-minimazation measures are applied in our protocol and can be found in chapter 6.4.1 'Summary of PRAC recommendations'.

This study aims to investigate the (cost-) effectiveness of UPA long term administration in comparison to *standard* treatment for patients with moderate to severe complaints due to uterine fibroids.

Study objective

This study has been transitioned to CTIS with ID 2024-512602-26-00 check the CTIS register for the current data.

Evaluate the (cost-) effectiveness of ulipristal in comparison with standard surgical treatment for symptomatic uterine fibroids, measured by the symptom severity score of the Uterine Fibroid Symptoms questionnaire (UFS-QOL), a validated Quality of life tool for fibroid symptoms. Also, a cost-effectiveness analysis will be performed.

Study design

Randomized controlled multi-center trial with 24 months of follow-up

Intervention

Ulipristal, 3-4x 3-month period of daily intake of one tablet of Ulipristal 5 mg, followed by a 2-month period of no intake.

Study burden and risks

The burden for the patients is mainly the completing of the questionnaires (baseline, 3, 6, 12, 18 and 24 months follow up) and the extra telephone appointment at 18 months of follow up. In the ulipristal group and the patients who had a myomectomy/embolization will have recurrent visits with their gynaecologist at 6 (only by telephone) 12 and 24 months of follow up. These visits are standard care and not extra in this study. Patients who had a hysterectomy will have telephone appointments at 6, 12, 18 and 24 months of follow up, this is extra in this study.

Recent post-marketing data showed a possible relation between ulipristal and a very rare form of liver injury, therefore riskminimazation measures were implemented (nationally), which have been applied in this trial to ensure safety. Therefore, this is also standard care, women not participating in this trial are also tested. The estimated risk is <1:95.000 patients. By monthly livertesting, the risk is minimized, as possible liver injury is traced in a very early stage.

The burden and chance on risks for the participating patients are very low. Both treatment options are widely implemented in the Netherlands en tested for safety in scientific research. Important to keep in mind is that both treatment options are implemented, but never compared to eachother. The extra burden is low, because both treatment options (also outside this trial) are accompanied by normal control visits and in case of ulipristal: regular bloodtesting. Patients allocated to the ulipristal group are not exposed to the risks that are asociated with surgery. Patients allocated to surgery are not exposed to the possible risk associated with ulipristal (most importantly: possible liver injury). For an extensive risk analysis we like to refer to the research protocol, chapter 13 'Structured Risk Analysis.

In chapter 8 'Methods' and the Patient information folder (pamflet), you can also find a clear schedule which appointments and procedures are standard care and which ones are extra in this trial.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Women visiting the gynaecological outpatient clinic with symptomatic fibroids will be screened for eligibility. In order to be eligible to participate in this trial, a subject must meet all of the following criteria:
- Symptomatic fibroids warranting surgical treatment, either hysterectomy, myomectomy or uterine artery embolization
- Conservative treatment failed or is undesired
- Pre-menopausal
- 18 years of age, or older

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
- Asymptomatic fibroids
- Current pregnancy or unwillingness to use contraception
- Suspicion of malignancy
- Current use of ulipristal
- Contra-indication for the use of ulipristal
o History of, or present liver disease or hepatic impairment;
o Transaminases (alanine transaminase (ALT) or aspartate aminotransferase (AST) and/or
total bilirubin exceeds 2 times the upper limit of normal (performed within a month prior to
inclusion).

o Medication that interacts with ulipristal:
* Moderate CYP3A4 inhibitors (e.g. erythromycin, grapefruit juice, verapamil)
* Potent CYP3A4 inhibitors (e.g. ketoconazole, ritonavir, nefazodone, itraconazole, clarithromycine)
* Potent CYP3A4 inducers (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, St. John*s wort, efavirenz)
- Not willing or able to give written informed consent

Study design

Design

Study phase:	4
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):	13-12-2018
Enrollment:	164
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Esmya
Generic name:	Ulipristal acetate
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	20-08-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-11-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-06-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-08-2019

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-11-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-06-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-06-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-09-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-09-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-02-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-03-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-10-2022

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-10-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-03-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-04-2024
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
EU-CTR	CTIS2024-512602-26-00
EudraCT	EUCTR2017-005120-16-NL
Other	Nederlands Trial Register: 6860
CCMO	NL62638.029.18