Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

STUDY PROTOCOL

TITLE

MyomaS Aspect Transformation at Ultrasound during Relugolix Estradiol Noretisterone treatment: MySaturn study.

ACRONYM: MySaturn

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Background and rationale

Background

Uterine fibroids (myomas) are benign tumors that develop from the smooth muscular tissue of the uterus. The prevalence of uterine fibroids rises with age, affecting up to 70% of women in their fifth-sixth decades. Risk factors are represented by African ethnicity, nulliparity, obesity, and diabetes. Although many fibroids remain clinically silent, approximately 25-50% of women develop significant symptoms. The clinical presentation may include one or more of the following symptoms: menorrhagia/metrorrhagia, chronic pelvic pain, dysmenorrhea, and "bulky" symptoms. The number, size and location of the fibroids determine the severity of symptoms, which may lead to severe impairment of quality-life and cause risks in terms of general and reproductive health [1].

Myometrial lesions are non-cancerous neoplasms in almost all cases. Actually, the prevalence of unexpected sarcoma in women undergoing surgery for a myometrial lesion ranges from 1/2000 to 1/350. Preoperative diagnosis of malignant mesenchymal tumors of the uterus (Mesenchymal Uterine Malignancies, MUMs) remains a significant challenge. Our group recently identified and validated a diagnostic algorithm based on women's clinical characteristics and specific ultrasound parameters, which showed high accuracy in evaluating suspicious myometrial lesions [2]. Although ultrasound is the first-level diagnostic tool to evaluate women with myometrial lesions, data on ultrasound features of MUMs are mainly based on retrospective case series. Similarly, accurate diagnostic criteria able to discriminate between benign and malignant lesions have never been prospectively validated with magnetic resonance imaging (MRI) [2].

Recently the MUSA (Morphological Uterus Sonographic Assessment) consensus statement proposed the terms, definitions and measurements that may be used to describe and report the sonographic features of the myometrium. Myometrial pathology may be localized (one or more lesions) or diffuse (when > 50 % of the myometrium is involved). Each identified lesion should be described according to its location, size and site. The minimum distance from the lesion to the endometrium (inner lesion-free margin) and to the serosal surface (outer lesion-free margin) of the uterus should be reported [2-3].

A uterine fibroid typically appears on ultrasound as a well-defined round lesion within the myometrium or attached to it, with variable echogenicity, often showing shadows at the edge of the lesion and/or internal fan-shaped shadowing. On color- or power-Doppler imaging, circumferential flow around the lesion is often visible [2-3]. Vascularization is typically low to moderate on color Doppler (color score 2-3). Conversely, irregular margins, cystic areas, heterogeneous echotexture, and increased vascularization are some of the characteristics suggestive for atypical or suspicious myometrial lesion [2].

Stratifying patients based on the risk of malignancy is crucial for deciding subsequent therapeutic approaches. Currently, a wide range of treatments (pharmacological, surgical, interventional radiology) is available for women with myometrial lesions. Decision-making should be guided not only by the risk of malignancy but also by the type of symptoms, the severity of the clinical condition, age, and reproductive desires.

In premenopausal women, when abnormal uterine bleeding is the predominant symptom, one of the most effective options is the combination therapy of relugolix (an oral GnRH receptor antagonist), estradiol, and norethisterone (Ryeqo®). This combination aims at suppressing the hypothalamic-pituitary-ovarian axis to induce amenorrhea while providing a minimal hormonal supply in order to prevent the effects of complete estrogen deprivation (vasomotor symptoms, vulvovaginal atrophy, bone mass reduction).

Previous clinical studies on this drug have focused on its efficacy in reducing menstrual blood loss and alleviating pain symptoms in women with symptomatic fibroids. In particular, phase III studies reported that over 70% of patients treated with this drug experience a reduction in menstrual bleeding within the first 24 weeks of therapy. Furthermore, the safety profile of the relugolix-estradiol-norethisterone combination appears favorable, with a low risk of severe adverse events and good long-term tolerability [4][5][6].
Currently, the effects of this treatment on fibroid size, uterine volume, and, most importantly, on the ultrasound features remain unclear.

Rationale
Based on the critical role of ultrasound evaluation in the diagnostic and therapeutic management of women with myometrial formations, the aim of this study is to analyze potential changes in ultrasound parameters during treatment with relugolix/estradiol/norethisterone. Specifically, the study aims at determining whether this pharmacological therapy can induce changes in myometrial formations that could impact patient stratification during the oncological risk assessment.

OBJECTIVES

Primary Objective

To observe the ultrasound features of myometrial lesions during treatment with relugolix/estradiol/norethisterone at baseline, and after 3 months, 6 months, and 12 months from treatment initiation, and to identify any change over time.

Secondary Objectives

To observe during treatment with relugolix/estradiol/norethisterone, the effect on symptoms (e.g., abnormal uterine bleeding, pelvic discomfort, urinary disorders, dyschezia, dyspareunia, chronic pelvic pain and to record any adverse effect of the drug.

METHODS

Study design
Monocentric, observational study, ambispective study

Target Population
Patients with ultrasound diagnosis of uterine fibroids, symptomatic for abnormal uterine bleeding, eligible for oral medical therapy with relugolix/estradiol/norethisterone. The retrospective cohort will be included starting from July 1st 2023.

Study duration
3 years (2 years for enrollment and 1 year for follow-up)

Inclusion criteria

1. Age ≥ 18 years.
2. Pre-menopausal status.
3. Ultrasound diagnosis of benign myometrial lesion.
4. Symptomatic patients presenting with abnormal uterine bleeding (menorrhagia/metrorrhagia).
5. Availability of ultrasound images in digital format.
6. Signature of Informed Consent

It is Specified that patients with a clinical indication for surgery may be included in the study if symptomatic for abnormal uterine bleeding.

Exclusion criteria

1. Age < 18 years.
2. Postmenopausal women.
3. Myometrial lesion ≤ 10 mm.
4. Myometrial formation suspected of malignancy on ultrasound (e.g., STUMP – Uterine Leiomyosarcoma).
5. Asymptomatic patients with uterine fibromatosis.
6. Personal history of malignant or premalignant uterine neoplasia (e.g., STUMPs, leiomyosarcoma, atypical endometrial hyperplasia, endometrial carcinoma, cervical carcinoma).
7. Patients with ovarian pathology.
8. Patients currently undergoing treatment for another malignancy.
9. Patients lacking available digital ultrasound images or whose image quality is insufficient to adequately characterize the target lesion's ultrasound features.

Suspicious myometrial lesions are defined based on clinical experience and according to the criteria established by the Mylunar study (2).

Variables and procedures

All women enrolled in the study will sign an informed consent form.
Patients retrospectively identified from the institutional registry may be included in the protocol if clinical data and ultrasound examinations are available, prior written consent. Recorded data will be retrieved from the examinations at baseline (before treatment) and 3 months, 6 months, and 12 months after treatment initiation.
Patients enrolled prospectively will be managed according to the activities and procedures depicted in Table 1. Clinical and ultrasound data will be recorded at baseline (before treatment) and 3 months, 6 months, and 12 months after treatment initiation.
Study data will be collected according to a dedicated eCRF that includes clinical, ultrasound, and pathological information (Appendix 1 MySaturn study).
The eCRF will be implemented using RED Cap platform (ref: https://projectredcap.org)
Study data will be collected and managed using REDCap electronic data capture tools hosted at Fondazione Policlinico Universitario A. Gemelli, IRCCS (https://redcap-irccs.policlinicogemelli.it/).
REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. People officially registered as study investigators or data managers will receive a user login to access the REDCap web platform and enter/manage data.

ENDPOINTS

Primary endpoint
Modifications in the volume of the index myometrial lesion during treatment with relugolix/estradiol/norethisterone;

Secondary endpoints (referred to the primary objectives)

Description of the ultrasound characteristics of the fibroids in the study population during treatment with relugolix/estradiol/norethisterone.
Based on current literature, the following features have been preselected for analysis:

- Max diameter of the index myometrial lesion
- Uterine volume
- Outer contour: regular or irregular;
- Echogenicity of the myometrial formation: mixed or homogeneous;
- Presence of cystic areas;
- Presence of acoustic shadows;
- Vascularization of the lesions, expressed on a 1 to 4 ordinal scale;
- "Cooked aspect."

Volume of the index myometrial lesion is considered the primary endpoint of this study and the other features as key secondary endpoints.

Secondary endpoints (referred to the secondary objectives)

Description of the clinical characteristics of the study population during treatment with relugolix/estradiol/norethisterone. The following clinical variables will be recorded:

- Effect on abnormal uterine bleeding, measured as the number of sanitary pads used during the cycle in patients who do not develop amenorrhea;
- Hemoglobin, serum iron, and ferritin levels at baseline, 3, 6, and 12 months;
- Dyspareunia, assessed using NRS or VAS scales;
- Chronic pelvic pain, assessed using NRS or VAS scales;
- Compression-related symptoms;
- Pollakiuria and dyschezia;
- Dyspareunia;

STATISTICAL ANALYSIS PLAN

Sample size calculation

Using a repeated measurements analysis of variance model for the primary endpoint with 4 time-points, a sample size of 111 patients will have a power=80% at a significance level of 5% to detect small effect size in term of f (f=0.10) assuming a correlation among repeated measures of 0.6.

Statistical analysis

Descriptive analyses of patients' characteristics will be provided. For continuous variables, the mean and standard deviation (SD) or the median and interquartile range (IQR) will be calculated as appropriate. The normality assumption about the distribution of continuous variables will be tested using the Kolmogorov-Smirnov test. Categorical variables will be summarized with frequencies absolute counts and percentages. Repeated measures ANOVA will be implemented to assess temporal trend in quantitative variables while dichotomous items will be analyzed using a mixed-effect generalized linear model. All statistical analysis will be performed using R software (www.r-project.org).

SAFETY

Definitions

Adverse event: any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.
Adverse reaction: a response to a medicinal product which is noxious and unintended. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Use outside the marketing authorisation includes off-label use, overdose, misuse, abuse and medication errors.
Serious adverse reaction: any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect or represents a new important medical event.

Regulatory management of adverse events

Any adverse event will be collected, recorded and assessed for seriousness and relatedness with study drug(s) or any other medicinal products in use, in order to identify suspected adverse reactions (ADRs).
All ADRs, regardless of the seriousness and expectedness, will be reported to National Competent Authority - AIFA, via the National Pharmacovigilance Network through the figure of Local Pharmacovigilance Responsible, as requested by the applicable law for the post-marketing pharmacovigilance activities (DM 30.04.2015 and GVP, module VI) and to the EC per local applicable rules. For the retrospective study with secondary analysis of clinical data, there is no further need of ADR reporting to national Competent Authority - AIFA, since all the reporting obligations have been fulfilled at the time of ADR presentation (DM 30.04.2015 and GVP module VI, section C 1.2.1.2.).

ETHICAL CONSIDERATIONS

Prior to initiation of a study site, the Sponsor will obtain approval from Ethics Committee to conduct the study in accordance with regulatory requirements. The study will be conducted in accordance with Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the declaration of Helsinki.

Informed Consent

Patients eligible for this study will be required to sign the Informed Consent Form in the context of a follow-up outpatient visit in which a study collaborator should be present. It will also be necessary to be able to use the data of patients who did not give Informed Consent because they are deceased, as failure to include this population would reduce the sample size producing negative consequences for the study in terms of significance of the results.
A copy of the written consent signed by the patient will be kept by the center in the appropriate section of the trial site file.

Confidentiality

Information about study participants will be kept confidential and managed under the applicable laws and regulations.
The investigator must ensure pseudonymized of the patients. Patients must not be identified by names in any documents submitted to the study promoter. Patient enrolment log must be kept strictly confidential to enable patient identification at the site
The investigator/institution should take measures to prevent accidental or premature destruction of these documents. Essential documents should be retained for a period of not less than seven years from the completion of the Clinical Trial.

Sponsorship and financing

The study is spontaneous, not sponsored by pharmaceutical companies.

Insurance

Given the observational nature of the study, no insurance policy will be necessary.

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