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GRACE-trial: a randomised active-controlled trial for vulvovaginal atrophy in patients with breast cancer on endocrine therapy – study protocol

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INTRODUCTION

Breast cancer is the most common cancer type in women worldwide. Due to hormone receptor positivity in the majority of the breast cancer tumours is endocrine therapy a crucial part in the treatment landscape of breast cancer. Endocrine therapy consists of the use of selective oestrogen-receptor modulators or aromatase inhibitors. These medicines generate a hypoestrogenic environment by reducing circulating oestrogen or by altering the effect of oestrogen on tissue cells by receptor blockade. As a common side effect, vulvovaginal atrophy occurs in the majority of patients with breast cancer using endocrine therapy. Vulvovaginal atrophy has a significant impact on physical and psychological well-being due to negative influence on quality-of-life, self-esteem and sexuality. As a consequence, adherence to endocrine therapy for the standard duration of 5–10 years is challenging, resulting in higher rates of therapy interruption, leading to poorer prognosis with shorter distant disease-free survival. The standard treatment for vulvovaginal atrophy in postmenopausal women is based on the use of local hormonal treatment. However, when a patient has a history of breast cancer, delay of treatment and undertreatment are ubiquitous.

Methods and analysis

In this first ever prospective randomised trial patients with breast cancer on endocrine therapy with vulvovaginal atrophy will be treated with the available local treatment modalities with a 1:1:1 randomisation: oestrogen, dehydroepiandrosterone, moisturisers and a co-treatment of oestrogen and probiotics. Patient-reported outcomes measurements will be implemented to investigate the efficacy of the implemented treatments. Safety of the treatments will be evaluated by assessing systemic sex hormones concentrations.

Ethics and dissemination

This study was approved by the Ethical Committee of Ghent University Hospital and by the Federal Agency for Medicines and Health Products. Results will be published in peer-reviewed journals and released in international conferences.

Trial registration number

2021-001921-31.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Randomised phase IV trial.
⇒ Implementation of an active control arm instead of placebo.
⇒ No blinding procedures in this trial, patient and physician know the treatment allocation.
⇒ Single-centre study with relatively small sample size.

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the importance of diagnosing and discussing symptoms of VVA in patients with breast cancer and in extent with all postmenopausal patients. The majority of patients with breast cancer on endocrine therapy will experience symptoms of VVA during endocrine therapy. Due to the occurrence of these symptoms, adherence to endocrine therapy in patients with breast cancer is challenged and high rates of interruption or termination of endocrine therapy are reported, impeding long-term prognosis of the patient.8

The standard treatment for VVA in postmenopausal women is based on the use of local hormonal treatment. Facing a history of breast cancer, patients will experience delay of treatment and undertreatment for VVA. Hesitance for discussing vaginal health and sexuality is a facilitator for the deprivation of VVA treatment along with reluctance of initiation of local hormonal treatment in breast cancer survivors.9 Besides moisturisers and local hormonal treatments, recent evidence points towards targeting the vaginal microbiome in order to restore vaginal health.10–12 Supplying probiotics can contribute in restoring and maintaining a healthy vaginal homoeostasis.13

At present, there is lack of large prospective randomised data on local treatments for VVA in patients with breast cancer, yet the available literature showed no increased recurrence risk for breast cancer and their use is supported by official guideline statements from organisations such as the American College of Obstetricians and Gynecologists.9 15

This randomised trial will assess prospectively four different treatment strategies for VVA, including moisturiser, local oestrogen, local oestrogen with probiotics and dehydroepiandrosterone (DHEA).

MATERIALS AND METHODS
Study design and objectives
GRACE-trial is a single-centre, prospective, randomised active-controlled clinical trial for the assessment of efficacy and safety of different available local treatment modalities in patients with breast cancer on endocrine therapy with VVA. Four different treatment modalities will be assessed in this clinical trial: oestrogen, DHEA, moisturisers and a co-treatment of oestrogens and probiotics. A study overview can be found in figure 1.

Ethics and dissemination
This study was reviewed and approved by the Ethical Committee of Ghent University Hospital (study number BC-09638, protocol V.1.0, approval on 22 October 2021) and by the Federal Agency for Medicines and Health Products (approval on 25 October 2021). Study results will be published in peer-reviewed journals and further disseminated at international conferences.

Study population and eligibility criteria
Patients with breast cancer on endocrine therapy (SERM or AI) with symptoms of VVA are the primary target population for this study.

A total number of 160 patients will be enrolled in this study (40 patients in each treatment group).

The eligibility criteria can be found in figure 2.
Recruitment and randomisation
Recruitment of patients will take place at Ghent University Hospital during routine follow-up appointments at one of the participating departments (Gynaecology, Medical Oncology and Radiotherapy). Initial screening will be performed by the treating physician. If a patient with breast cancer on endocrine therapy with symptoms of VVA is seen on a routine follow-up breast cancer consultation, the study will be introduced and the patients interested in the study will be referred to the study team for evaluation of inclusion and exclusion criteria.

Randomisation will be performed electronically through a computer-driven randomisation list. No stratification factors will be implemented. There is no blinding of treatment for participant or investigator. Withdrawn subjects will be replaced until the predefined goal of 160 subjects have completed the study. If the following data and samples are available, the subject will not be replaced: at least two patient-reported outcome measure (PROMs) assessments, at least two serum samples and two vaginal microbiome samples.

Trial status
Recruitment is ongoing and started in March 2022 and is expected to be completed in March 2026.

Allocation and initial assessment
The study team will contact the patient and a prescreening with control of eligibility criteria will be performed. When a patient is eligible, a first study visit will be planned. Initial assessment will be performed at the first study visit after agreement and signing the informed consent file. Patients will be allocated to a treatment group based on the result of the randomisation process.

Data management and monitoring
Registered study data will be stored digitally, using Research Electronic Data Capture (REDCap, Nashville, USA). Data will be not be publicly available and stored securely at the study centre. Adverse events and serious adverse events will be reported. All serious adverse events (initial and follow-up information) occurring during this study will be reported within 24 hours to the Clinical Trial Unit of Ghent University Hospital. The latter will be responsible for data monitoring.

Primary objectives
Three primary objectives have been determined. The efficacy of the different treatment modalities will be assessed by means of the first two primary objectives. The first primary objective is the assessment based on PROMs. The second primary objective is the clinical evaluation by means of vaginal pH and the Vaginal Maturation Index, the latter being a direct microscopical evaluation of the vaginal epithelium using a vaginal smear sample.

Lastly, the third primary objective is the evaluation of systemic sex hormone concentrations. This objective is frequently used to address safety in regard to sustained systemic elevations of these hormones.

Secondary objectives
The secondary objective in this study is the characterisation of vaginal microbial alterations after treatment initiation. Identification of these alterations can help in further understanding of the pathophysiology of VVA and potentially create opportunities for new treatment strategies towards VVA in patients with breast cancer on endocrine therapy.

Study treatment
Patients will be allocated to one of four treatment arms, with 40 patients to be enrolled in each arm. All treatment groups will receive a topical (vaginal) treatment for VVA for 12 weeks. An overview of treatment regimens can be found in figure 1.
Group A will receive 0.03 mg oestriol (Oekolp, Dr KADE Pharmazeutische Fabrik, Berlin, Germany) in a regime of one vaginal ovule daily for three consecutive weeks, followed by one vaginal ovule two times per week. Group B will receive 6.5 mg prasterone (DHEA) (Intrarosa, Basic Pharma Manufacturing, Geleen, The Netherlands) in a regime of one vaginal ovule daily. Group C will receive a moisturiser treatment, based on hyaluronic acid (Premeno Duo, DeltaMed, Friedberg, Germany) in a regime of one vaginal ovule daily (figure 1).

**Interventions**

Enrolled patients will have three study visits. Study visits will be organised at baseline, after 6 weeks (±14 days) and after 12 weeks (±14 days, end of study). On these study visits the following interventions will be performed (figure 1).

**Vaginal assessments**

These will include vaginal pH measurement using a pH indicator strip (art. 662-0201, Macherey-Nagel, Düren, Germany) after insertion of a non-lubricated strip against the mid-vaginal lateral wall for 10 s. After measuring the vaginal pH, a vaginal sampling brush (Viba-Brush, Rovers Medical Devices, Oss, The Netherlands) will be used to gently scrape the upper third of the vaginal wall to obtain exfoliating squamous cells to assess the Vaginal Maturation Index. The Vaginal Maturation Index represents the proportion of parabasal, intermediate and superficial squamous cells. Using a predefined formula ($0.2 \times \% \text{ parabasal cells} + 0.6 \times \% \text{ intermediate cells} + 1.0 \times \% \text{ superficial cells}$), a qualitative indicator for oestrogenic effect on the vaginal epithelium can be obtained.

**Venous blood sampling**

Due to the low concentrations, general laboratory tests of sex steroids are inadequate for the evaluation of possible alterations in these concentrations, except for dehydroepiandrosterone sulphate (DHEA-S) which is abundantly present in serum. Previous work already indicated the strength and importance of measurements by mass spectrometry (liquid chromatography with tandem mass spectrometry (LC-MS/MS)) in order to achieve competent assessment of concentration variations. The following sex steroid concentrations will be determined: oestrone, oestradiol, DHEA, DHEA-S, testosterone and dihydrotestosterone.

**Mid-vaginal swab**

This will be used for microbial analysis. After collecting the swab, the sample will be stored at ~80°C until processed. Bacterial DNA will be extracted and the microbiome will be characterised using cpn60 sequencing metagenomics as previously described.

**PROMs**

Apart from these clinical interventions, patients will also be required to fill in questionnaires for PROM assessment, using EQ-5D-questionnaire and the FACT-ES questionnaire.

**Data analysis**

**Sample size**

Given the lack of direct comparative studies between the included treatments, we based our sample size calculation on the only available retrospective review that compares DHEA and oestrogens with placebo, although not in a direct comparison but through retrospective interstudy comparison. In this review, the difference of effect of DHEA and oestrogen to placebo in previous studies was compared using severity scores for vaginal dryness. DHEA improved the severity score in three studies with a mean of 0.33 compared with placebo, while this was 0.40 for oestrogen. Using these numbers, aiming for a power of 90%, a sample size of 12 for each group would be needed. However, due to lack of prospective comparative data, we will increase our sample size to 40 patients in each group to overcome potential lower differences, yet we acknowledge that this is an arbitrary chosen increase.

**Statistics**

Descriptive statistics will be implemented (number of observations, mean, SEM). Comparison of treatments will be based on t-tests, analysis of variance and, for sex steroid concentrations, analysis of covariance with the baseline concentration as covariate.

**Patient and public involvement**

Patients were involved in the design of this research, where the research question, implemented questionnaires and outcome measures were discussed.

**DISCUSSION**

At present, patients with breast cancer with VVA are inadequately treated for this common side effect of endocrine therapy. A direct head-to-head comparison for efficacy is lacking, therefore it was chosen as one of our primary objectives. With this comparison we aim to clearly distinguish the magnitude of treatment efficacy between the different modalities. In close relationship with efficacy resides the question of safety with regard to breast cancer recurrence. Systemic alterations of sex steroid concentrations have previously been described where the magnitude of these alterations depend on the implemented treatment modality. No increased recurrence has been described after initiation of local treatment for VVA. With this direct comparison we aim to objectify the relative magnitude of alterations of sex steroid concentrations. This new information may contribute to the increase of awareness and may help clinical decision-making, possibly

generating a lower threshold for clinicians to start treatment for VVA in patients with breast cancer. This in turn may improve adherence to endocrine therapy which is a prerequisite for its success. Non-adherence to endocrine therapy is driven by the side effects of this treatment.

The vaginal microbiome fulfills a crucial role in the vaginal homeostasis. Previously, differences in the vaginal microbiome of postmenopausal women with and without VVA have been identified. Microbial changes induced by treatment will be evaluated in this study. Furthermore, we implement probiotics in combination with oestrogen in the vaginal treatment of VVA. Previous work demonstrated the safety and efficacy of this combination treatment of bacterial vaginosis. Previous results of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: atlas, a randomised trial. Lancet 2013;381:805–16.


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