A two-part (observational and intervention) study to explore disease characteristics of vulvar (pre)malignancies compared to healthy volunteers.

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Primary Objectives- To evaluate disease related characteristics in patients with different vulvar conditions compared to healthy volunteers - To evaluate the variability of the selected biomarkers between subjects, and within subjects over time....

Ethical review	Approved WMO
Status	Completed
Health condition type	Reproductive neoplasms female malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON54913

Source
ToetsingOnline

Brief title
Deep phenotyping of vulvar (pre)malignant disease.

Condition

- Reproductive neoplasms female malignant and unspecified
- Epidermal and dermal conditions

Synonym
vulvar (pre)malignancies, vulvar cancers

Research involving
Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research
Source(s) of monetary or material Support: CHDR funded study

Intervention

Keyword: disease characteristics, vulvar (pre)malignancies

Outcome measures

Primary outcome

* Punch biopsies: histology (e.g. H&E and HPV typing), IHC (e.g. p16 and p53), mRNA extraction

* Vulvar pH*

* Hormonal status (FSH, LS, estrogen)

* DermaToolbox:

- 2D photography* (photo documentation)

- 3D photography* (lesion dimensions)\ - Dermoscopy* (erythema + roughness scores)

- Optical Coherence Tomography* (skin morphology, skin layer thickness, blood perfusion)

- Confocal Microscopy* (skin morphology)

- Ultrasonography* (skin morphology, skin layer thickness, tumour penetration up to 4cm)

- Trans Epidermal Water Loss* (skin barrier function)

* Clinical scores (e.g. Günthert, RECIST, PROVOKE)

* Patient reported outcomes* (this may include, but is not limited to: NRS pruritus, NRS burning sensation, NRS pain, sleeplessness QoL, patient

satisfaction scores of imaging tools)

Secondary outcome

* Vulvar, vaginal and anal swabs* for microbiome

Study description

Background summary

A wide spectrum of benign and (pre)malignant lesions may occur in the anogenital region. For example, lichen sclerosis (LS) is a chronic inflammatory dermatitis with a predilection for the anogenital area. This disease can cause severe atrophy in this area and lead to deformities of the vulvar structures. It is mainly a pruriginous condition but can also be asymptomatic. The median age at time of LS diagnosis is around 65 years and the prevalence is increasing with age up to 1:30 women. Most important, LS is associated with an enormous morbidity and an increased risk of vulvar premalignancy (dVIN) and subsequent cancer (4-6%).
The cornerstone of treatment for vulvar (pre)cancers is surgery. Surgical treatment in the vulvar area is frequently associated with significant morbidity due to damage to vital structures like urethra, vagina, clitoris and anus. Correct distinction between healthy and (pre)malignant tissue is one of the major challenges for the clinician. Incorrect identification of (pre)cancerous lesions results in re-excisions, recurrences, metastases and worse prognosis. This underlines the high unmet medical need for clinicians to better discriminate vulvar (pre)cancers.
In addition, most clinical trials within the vulvar cancer field make use of clinical outcomes, as physician-evaluated scores, in the assessment of drug efficacy. These outcomes can give a crude estimation of the disease *severity* and potential improvement during the clinical trials. However, these clinical endpoints have disadvantages as limited objectivity due to a possible response quantification bias by the scoring physician, potential inter-rater variability and lack of sensitivity needed to quantify smaller effects of a novel drug. Unfortunately, there is little research on the mechanisms underlying the development of and the response to treatment in vulvar (pre)cancers. Therefore, more objective endpoints are needed to support unbiased objective evaluation of drug efficacy in this field.
In this study a multi-modal and in-depth approach will be used, which consist of different measurement methods and imaging techniques to acquire non-physician based disease-related outcomes of vulvar (pre)malignancies. For example, invasive punch biopsy will be compared to different non-invasive techniques such as 2D/3D photography, dermoscopy, optical coherence thomography (OCT), ultrasonography and trans-epidermal waterloss (TEWL) (Figure 1). By

integrating data from different domains such as biophysical, imaging, molecular, cellular and microbial, a so-called *systems dermatology* approach is used. The biomarkers created by these different technologies will describe the pathophysiology in high detail and support a holistic view on vulvar disease and potential drug mechanisms.
Therefore, a two-part study is proposed. Part 1: a non-interventional clinical study to characterize different vulvar conditions, including lichen sclerosus and (pre)cancerous lesions (HSIL), in comparison to healthy controls. Part 2: an interventional clinical study in vulvar lichen sclerosus (LS) patients treated with topical clobetasol, to observe whether different sampling methods and non-invasive imaging techniques can discriminate the responsiveness to change in disease activity. The results/endpoints from this study can be used in the future for research into new treatments for these different vulvar conditions. The results will be analysed and integrated with a novel machine learning approach.

Study objective

Primary Objectives
- To evaluate disease related characteristics in patients with different vulvar conditions compared to healthy volunteers
- To evaluate the variability of the selected biomarkers between subjects, and within subjects over time.

Secondary Objectives
- To evaluate the feasibility, suitability and potential use of the skin microbiome as biomarker for early phase clinical drug development in patients with different vulvar conditions and to compare with healthy individuals.

Exploratory Objectives
- To design a machine learning model for diagnosis of vulvar (pre)malignant disease by combining individual biomarker assessments.

Study design

This is an prospective two-part (observational and intervention), open label, non-comparative and exploratory phase I study to evaluate the applicability and integration of novel biomarkers in patients with vulvar (pre)malignancies.

Part A. This is an observational study in up to 40 patients with different benign and (pre) malignant vulvar conditions (vulvar HSIL (n=10), vulvar LS (n=10), VSCC (n=10) and 10 healthy volunteers. All participants will visit CHDR for a screening and 5 short visits (day 1 (baseline), 2 and 8 (end of study)).

Part B. This is an interventional and open label study with a topical steroid in vulvar LS patients (the LS patients from part A roll over to part B). 10

Patients with vulvar LS will treat their lesion(s) from day 8 until day 36. Hereafter, a follow-up visit will take place at Day 22 and a final follow-up visit will take place at day 36.

Intervention

Clobetasol propionate ointment

Study burden and risks

The overall aim of this study is to evaluate objectively measured disease related characteristics in patients with different vulvar conditions compared to healthy volunteers.

Benefit
No medical benefit can be expected during the observational part of this study for the participating subjects.

Risks
- Although it is a minimal invasive procedure, participants can experience pain and/or a haematoma in rare cases during and after biopsy of the vulvar area and/or venepuncture.
- Patients could experience a (temporary) flare-up of their disease related symptoms due to interruption or postponement of their standard treatment.
- LS patients will apply clobetasol for two weeks. Clobetasol is an EMA-approved ointment for treatment of LS. For LS patients treated with clobetasol no long-term benefits are expected if only treated for 2 weeks. On short term, a reduction in itch and pain could be observed. Possible although rare local adverse effects are local burning sensation and itching during application. For a structured risk assessment see the SmPC of Clobetasol

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Non-pregnant female subjects, 25-95 years of age (inclusive); in general, stable good health as per judgment of the investigator based upon the results of a medical history, physical examination (BMI * 30) and vital signs.
2. BMI of * 30
3. If female of childbearing potential, have a negative urine pregnancy test at Day 0.
4. Willing to give written informed consent and willing and able to comply with the study protocol.
5. Ability to communicate well with the investigator in the Dutch or English language.
6. Subject is willing to undergo vulvar biopsies.
7. Subject is willing to refrain from washing (including bathing, swimming, showering and excessive sweating) the vulva counting from midnight of every study visit day.
8. Subject is willing to refrain from application of products (e.g. ointments, crème or wash) on the vulva 24 hours prior to every study visit day.
9. Subject is willing to refrain from sexual intercourse less than 24 hours prior to every study visit.
10. Subject is willing to refrain from shaving, waxing or other hair removing treatments in the perineal area in the 24 hours prior to every study visit.
11. Willing to refrain from any active treatment for vulvar HSIL and LS as from 14 days prior to Day 0.

Eligible HSIL patients must meet all of the following inclusion criteria at screening:
12. At least one sharply marginated lesion (plaque) that can be accurately

measured (using RECIST criteria), in at least one dimension with a smallest diameter of *15 mm, with confirmed HSIL diagnosis by histologic confirmation. This histologic diagnosis does not necessarily have to be performed close to inclusion.

Eligible LS patients must meet all of the following inclusion criteria at screening:
13. Clinically and/or histologically diagnosed with LS and under topical treatment with topical corticosteroids or willing to start topical steroid treatment during study participation.

Eligible VSCC patients must meet all of the following inclusion criteria at screening:
14. Histologically confirmed primary or local recurrent VSCC.

Exclusion criteria

1. Significant, uncontrolled or unstable disease in any organ system as per judgment of the investigator (regardless of association with the immunosuppressing disorder/therapy), including but not limited to: psychiatric, neurologic, cardiovascular, pulmonary, gastrointestinal, hepatic, renal, endocrine, hematologic or respiratory disease.
2. History of immunological abnormality (e.g., immune suppression) that may interfere with study objectives, in the opinion of the investigator.
3. Known infection requiring (topical or oral) antibiotic therapy within 28 days prior to Day 0;
4. The use of any oral/systemic medication (e.g. immunomodulatory, immunosuppressive, acetylsalicylic acid) within 28 days prior to Day 0, if the investigator judges that it may interfere with the study objectives. The use of paracetamol (up to 4 g/day) is allowed;
5. Pregnant, a positive pregnancy test, intending to become pregnant, or breastfeeding;
6. Self-reported: (a) immunocompromised state, (b) sexually transmitted disease, (c) AIDS and/or (d) hepatitis.
7. Have any current and / or recurrent clinically significant or subject reported skin condition in the vulvar area other than the (absence of) vulvar disease wherefore subject is included in the study.

Eligible vulvar patients must meet none of the following exclusion criteria at screening:
8. Have any current relevant (inflammatory) skin infections in the treatment area other than the observational disease (vulvar LS, vulvar HSIL of VSCC), inclusively, but not limited to atopic dermatitis, herpes, candidiasis or psoriasis.
9. Have used or received any topical vulvar HSIL treatment, laser therapy or

surgery in the anogenital area within 28 days prior to Day 0
10. Have used or received any topical corticosteroids or other topical immune suppressive treatment for LS within 14 days prior to Day 0
11. Have used or received chemo-or radiotherapy or surgery in the anogenital area within 3 months prior to enrolment.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Diagnostic

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	16-02-2021
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Clobetasol propionate ointment
Generic name:	Dermovate Ointment
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	17-07-2020
Application type:	First submission

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	14-12-2020
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	09-04-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	14-05-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 23864
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2020-002201-25-NL
CCMO	NL73964.058.20

Study results

Date completed: 15-10-2021

Results posted: 31-08-2022

First publication
25-08-2022