Predicting Response In Cervical intraepithelial neoplasia to Topical Imiquimod treatment (PRedICT-TOPIC)

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This study aims to validate the potential of immune related biomarkers to predict the clinical response of patients with primary cHSIL to imiquimod and aims to explore the value of these immune biomarkers in recurrent/residual cHSIL to predict...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Cervix disorders (excl infections and inflammations)
Study type	Observational invasive

Summary

ID

NL-OMON51652

Source
ToetsingOnline

Brief title
PRedICT-TOPIC

Condition

- Cervix disorders (excl infections and inflammations)

Synonym
cervical high squamous intraepithelial lesion (cHSIL) / CIN

Research involving
Human

Sponsors and support

Primary sponsor: Catharina-ziekenhuis
Source(s) of monetary or material Support: ZonMW

Intervention

Keyword: Cervix, CIN, HSIL, Imiquimod

Outcome measures

Primary outcome

• Confirm the relationship between a complete clinical response to imiquimod and the increased stromal infiltration of CD4+ T cells, CD11c+ cells and/or M1-like macrophages as well as the decreased infiltration with FoxP3+ Tregs in primary cHSIL.

• Validate the association of a *hot signature*, defined as the sum of the numbers of stromal CD4+/CD11c+/M1+ cells per square millimeter minus the number of stromal FoxP3+ cells per square millimeter, with a complete response to imiquimod treatment in primary cHSIL.

• Determine the sensitivity and specificity of the *hot signature* in patients with primary cHSIL lesions to estimate the predictive value for therapy efficacy upon imiquimod treatment.

Secondary outcome

• Explore the *hot signature* as a predictive biomarker for therapy efficacy to imiquimod treatment in patients with residual/recurrent cHSIL (rrcHSIL).

• Explore the *hot signature* as a predictive biomarker for spontaneous regression of cHSIL (e.g. CIN2).

• Determine treatment efficacy, HPV clearance, therapy adherence and reported side effects upon imiquimod therapy.

• Evaluate maintenance of lesion regression after imiquimod treatment by determination of recurrent cHSIL or progression to cervical cancer and time to

recurrence/progression.

• Explore and evaluate other potential more specific predictive (immune) biomarkers in cHSIL which are easily accessible and readily implemented for clinical prognosis, including dedicated gene expression profiles by Nanostring and gene methylation assays.

• Develop a simplified pathological scoring system by explorative development of a simplified dual immunohistochemistry protocol to identify the hot signature and exploration of the predictive value of this *immunoscore* in cHSIL.

• Validate the *hot signature* defined as epithelial or stromal CD4+/CD11c+/CD68+ cells via single immunohistochemistry per square millimeter with a complete response to imiquimod treatment in primary cHSIL

• Determine the vaginal microbiome in cHSIL patients treated with imiquimod or not treated to explore the potential interaction of the vaginal microbiome and composition of immune infiltrates and the relation to imiquimod treatment and relation to spontaneous regression.

Study description

Background summary

A persistent high risk Human Papilloma Virus (hrHPV) infection can cause (pre)malignant anogenital lesions of the cervix, vulva or vagina. Cervical high grade squamous intraepithelial lesions (cHSIL) have a malignant potential and require adequate therapy. The natural history of cHSIL is unpredictable: ~25% of cHSIL will regress, while 18% will progress to invasive cervical cancer. The standard treatment of histologically confirmed cHSIL is surgical excision by large loop excision of the transformation zone (LLETZ), with potential complications, such as hemorrhage, infection and an increased risk of preterm

birth in subsequent pregnancies. Imiquimod cream has been studied as a non-invasive treatment alternative and in our recent TOPIC-3 study for cHSIL we report a complete response rate of 55% upon imiquimod therapy. Imiquimod is now considered as a standard non-surgical therapy for patients with cHSIL in the Netherlands, especially in those patients with a future pregnancy wish. Side-effects of imiquimod therapy however are common and can be extensive, consisting mostly of local inflammation and burning, but also systemic adverse events such as headache and flu-like symptoms. Therapy adherence is challenging with up to 20% discontinuation of treatment due to the side effects and the 16 week treatment duration. As such, biomarkers which can predict response to imiquimod therapy are warranted, to increase therapy efficacy and to avoid side effects in patients who will not respond. Our previous work shows that clinical response to imiquimod in cHSIL is associated with a coordinated pre-existing type 1 T cell- and inflammatory myeloid cell infiltration and provided the first set of parameters that potentially can function together as a predictive biomarker CIBI (CHSIL Immune Biomarker for Imiquimod (CIBI)).

Study objective

This study aims to validate the potential of immune related biomarkers to predict the clinical response of patients with primary cHSIL to imiquimod and aims to explore the value of these immune biomarkers in recurrent/residual cHSIL to predict treatment responses for imiquimod and aims to explore theit*s potential in spontaneous regression of cHSIL (CIN2).

Study design

Multicenter, real-life prospective cohort validation study.

Study burden and risks

The burden associated with participation to this study is minimal since patients are included in accordance to real-life selection. If patients prefer imiquimod treatment for the therapy for their cHSIL lesion after consultation with the gynecologist they will be treated following a standard protocol, following the national guideline for cHSIL (CIN, AIS en VAIN.pdf). The burden for patients to participate in the study lies in an extra biopsy taken at colposcopy at 20 weeks and taking vaginal cultures for microbiome analysis. The benefit for the patients lies in extra support via telephonic consultation and close monitoring. For the patients in the observational arm with no treatment, no extra examinations will be performed according to the national guideline for cHSIL, only data and tissue will be used and two vaginal swabs taken. For the study cohort the benefit is limited but if we are able to identify a clinical predictive biomarker for spontaneous regression or imiquimod in cHSIL, this may increase therapy efficacy for future cHSIL patients by patient selection preventing unnecessary (imiquimod) therapy.

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

- Primary cHSIL lesions (e.g. CIN3 or CIN 2), histologically confirmed by diagnostic biopsy
NB: In case of CIN 2, <30 years, expectative management must be discussed according to the Dutch national guideline with the patient, if the patient prefers imiquimod therapy the patient can be treated with imiquimod and enrolled in the study, if the patient prefers expectative management they can be enrolled in the observational CIN 2 arm.
- Recurrent or residual cHSIL lesions after initial LLETZ treatment (e.g. CIN2 or CIN3), histologically confirmed by diagnostic biopsy
- Age of 18 years or older

Exclusion criteria

- Concomitant diagnoses of VAIN (vaginal intraepithelial neoplasia e.g. vaginal HSIL)
- PAP 4 cytology as indication for the baseline colposcopy at study entrance
- Adenocarcinoma in situ (AIS) diagnosis
- Previous imiquimod therapy for cHSIL
- previous cervical malignancy
- current malignant disease
- immunodeficiency (including HIV/AIDS and immunosuppressive medication)
- pregnancy
- legal incapability
- insufficient knowledge of the Dutch language

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	30-06-2022
Enrollment:	410
Type:	Actual

Ethics review

Approved WMO

Date:	23-05-2022
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	08-07-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-08-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-12-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-02-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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
CCMO	NL79879.100.22