Safety, immunogenicity and clinical response of sig-HELP-E6SH/E7SH-kdel, injected in the epidermis by DNA tattoo, in HPV16-positive vulvar intraepithelial neoplasia: a phase I/II study

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* To study the safety of two naked DNA vaccines encoding sig-HELP-kdel and shuffled HPV16 E6 or E7 gene products (sig-HELP-E6SH/E7SH-kdel). * To study the systemic HPV-specific immune response of sig-HELP-E6SH/E7SH-kdel.

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

Summary

ID

NL-OMON47893

Source
ToetsingOnline

Brief title
HPV16 E6-E7

Condition

- Reproductive neoplasms female benign

Synonym
uVIN, vulvar dysplasia

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: Europese Unie

Intervention

Keyword: HPV16, Immunogenicity, Safety, uVIN

Outcome measures

Primary outcome

* To study the systemic HPV-specific immune response of two naked DNA vaccines encoding sig-HELP-kdel and shuffled HPV16 E6 or E7 gene products (sig-HELP-E6SH/E7SH-kdel).

Secondary outcome

* To study the safety of sig-HELP-E6SH/E7SH-kdel.

* To study the clinical response to vaccination of sig-HELP-E6SH/E7SH-kdel.

Exploratory objectives:

* To study the migratory capacity of HPV16-specific T cells by analysis of their presence in vaccine sites.

* The effect of vaccination on the immune infiltrate in VIN lesion microenvironment will be determined by multicolour fluorescent immunohistochemistry.

Study description

Background summary

Human papilloma virus (HPV) infection is strongly associated with the

development of squamous cell cancer in the
anogenital and head and neck region. HPV16 infection may also cause a chronic skin disorder of the vulva known as
vulvar intraepithelial neoplasia (VIN). Patients often have a weak or no spontaneous HPV-specific T cell response which is
thought to be important in the clearance of infection and disease. VIN is a chronic disease with high relapse rates after
standard treatments. Spontaneous regression are found in 1.2% op patients. Because the persistence of oncogenic HPV
proteins E6 and E7 is required for carcinogenesis, these viral antigens are exquisite targets for immunotherapeutic
interventions.
Here we propose to initiate a phase I/II study in patients with HPV16-positive uVIN lesion using a novel and potent
intradermal HPV DNA vaccination strategy. In preclinical studies this strategy was shown to be much more potent in the
induction of E6 and E7-specific CD8+ cytotoxic T-cell immunitiy than existing DNA vaccination strategies, providing a
strong rationale for its clinical evaluation. In this phase I study we will define the safety, toxicity and immunogenicity of this
highly promising DNA vaccination strategy in patients with a HPV-positive uVIN lesion. This study will allow us to define
the value of this novel DNA vaccination strategy for the treatment of HPV-associated (pre)malignancies.

Study objective

* To study the safety of two naked DNA vaccines encoding sig-HELP-kdel and shuffled HPV16 E6 or E7 gene products (sig-HELP-E6SH/E7SH-kdel).
* To study the systemic HPV-specific immune response of sig-HELP-E6SH/E7SH-kdel.

Study design

This is a single centre, non-randomized Phase I/II study. Patients with HPV16+ VIN lesions will be enrolled.
The first cohort of patients (n=5) will receive 4 intradermal injections of 2 mg sig-HELP-E6SH/E7SH-kdel on days 0, 14, 28 and 42. Just before administration, 1 mg of sig-HELP-E6SH-kdel will be mixed with 1 mg of sig-HELP-E7SH-kdel to have 2 mg of the combined E6SH/E7SH. After all 5 patients received all vaccination, we will perform an interim analysis by flow cytometry. There are 2 possible scenarios after the interim analysis:
1. Acceptable immune response
2. Non acceptable immune response
Depending on the outcome of the interim analysis we will continue with the second cohort of patients.

1. Additional cohort of 9 patients
2. Termination of the trial

Intervention

Sig-HELP-E6SH/E7SH-kdel will be injected intradermally on days 0, 14, 28 and 42 using a permanent make-up device (Derm.MT GmbH, Berlin, Germany).

Study burden and risks

Patients will be vaccinated 4 times with sig-HELP-E6SH/E7SH-kdel using a permanent make-up device. Further, they will undergo 5 bloodtests, 5 urinetests, 2 times a skin biopsy and twice a biospy of the VIN lesion. They will come 11 times to the outpatients clinic for the before mentioned tests and physical examinations. See appendix I in the protocol for the complete schedule.
The vaccine that is being used in this clinical trial does not contain factors favoring integration, nor does it contain sequences that can lead to replication, or that can become part of viruses or bacteria. Preclinical data show that intradermal DNA vaccination is much more potent than classical intramuscular injection. Tattooin of skin is a commonly used method for treatment of scars or as part of reconstructive surgery. Tattooing may induce a burning sensation during tattooing, which will stop the moment the tattooing is ended. Furtermore, flulike symptoms with fever during 48 hours after vaccination can occur.
This investigation can lead to a more effective therapy for patients with HPV-associated (pre)malignincies. There are no persistent or severe side effects known for this treatment. Therefor we consider the physical discomfort associated with participation in this study as acceptable.

NB Update 11-01-2019: No skin biopsies from vaccination site are taken anymore, due to unability to culture T-cells from the tissue and extra burden for the patient

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

* Age above 18 years
* Willing and able to undergo the planned study procedures
* Written informed consent
* Histologically proven visible uVIN lesion (histology *3 months prior to enrolment and at least 6 weeks after last treatment)
* HPV16-positive VIN lesion (to be determined on archival tumour tissue (*10 years old); if not available a new biopsy will be required)
* No indication of an active infectious disease: HIV, HCV and HBV negative
* No history of autoimmune disease or systematic undercurrent disease which might affect immunocompetence
* Adequate bone marrow (WBC > 3.0/nL, platelets > 100/nL), renal function (creatinine clearance > 40 mL/min), and liver function (bilirubin < 1.5 x ULN, normal blood coagulation)

Exclusion criteria

* Prior treatment with anti-HPV agents
* Participation in a study with another investigational drug within 30 days prior to enrolment in this study
* Severe cardiac, respiratory, or metabolic disease

* Use of systemic steroids or other immunosuppressive drugs
* Use of oral anticoagulant drugs (except ascal)
* Severe infections requiring antibiotics
* Any treatment for the uVIN lesion within 6 weeks prior to the enrolment (including imiquimod)
* Lactation or pregnancy (if applicable)
* Not willing to take adequate contraceptive measures (if applicable)

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-12-2016
Enrollment:	14
Type:	Actual

Ethics review

Approved WMO Date:	14-01-2016
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	30-08-2016
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO

Date:	29-01-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-05-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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
EudraCT	EUCTR2015-005339-42-NL
CCMO	NL55908.000.15