Safety, toxicity and immunogenicity of HPV16 E7 DNA vaccination in HPV16+ vulvar intraepithelial neoplasia grade III: a phase I study.

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To study the safety, toxicity and immunogenicity of a naked DNA vaccine encoding the shuffled HPV16 E7 gene product (TTFC-E7SH) in patients with HPV16+ VINIII lesions.

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

Summary

ID

NL-OMON40423

Source
ToetsingOnline

Brief title
SEVEN

Condition

- Reproductive neoplasms female benign

Synonym
VINIII, 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, VINIII

Outcome measures

Primary outcome

• To study the safety and toxicity of two different doses of the naked DNA

vaccine encoding the shuffled HPV16 E7 gene products (TTFC-E7SH).

• To study the HPV-specific immune response in two different doses of

TTFC-E7SH.

Secondary outcome

• To study the clinical response to vaccination of two different doses of

TTFC-E7SH

Exploratory objectives:

• Local immune response

HPV16-specific proliferative capacity will be tested in triplicate in a 3 day

proliferation assay.

• Tumour microenvironment

The effect of vaccination on the tumour 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 study in patients with HPV16-positive VINIII 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 VINIII lesion. This study will allow us to define the optimal dosage and value of this novel DNA vaccination strategy for the treatment of HPV-associated (pre)malignancies.

Study objective

To study the safety, toxicity and immunogenicity of a naked DNA vaccine encoding the shuffled HPV16 E7 gene product (TTFC-E7SH) in patients with HPV16+ VINIII lesions.

Study design

Phase I immunogenicity/toxicity-evaluation in 12 patients.

Intervention

TTFC-E7SH will be injected intradermally on days 0, 3 and 6 using a permanent make-up device, and boost vaccinations will be given after 4 weeks (day 28, 31 and 34).

Study burden and risks

Patients will be vaccinated 6 times with TTFC-E7SH using a permanent make-up device. Further, they will undergo 5 bloodtest, 3 urinetest, 3 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 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.

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

* Age above 18 years
* Willing and able to undergo the planned study procedures
* Written informed consent
* Histologically proven visible VINIII lesion (last histology <=3 months prior to enrolment)
* HPV16+ VINIII lesion (to be determined on archival tumour tissue (<=10 years old); if that is not available a biopsy will be required)
* No indication of an active infectious disease
* No history of autoimmune disease or systemic undercurrent disease which might affect immunocompetence
* Adequate bonemarrow, renal function and liver function

Exclusion criteria

* Prior treatment with anti-HPV agents
* Participation in a study with another investigational drug within 30 days prior to the enrolment in this study
* Severe cardiac, respiratory or metabolic disease
* Use of steroids or other immunosuppressive drugs
* Use of oral anticoagulant drugs
* History of a malignancy except curatively treated low-stage tumour
* Severe infections requiring antibiotic
* Any treatment for the VINIII lesion within 6 weeks prior to enrolment
* 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:	Completed

Start date (anticipated):	12-06-2014
Enrollment:	12
Type:	Actual

Ethics review

Approved WMO Date:	27-02-2014
Application type:	First submission
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

ID: 27857
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2013-000610-38-NL
CCMO	NL46637.000.13
OMON	NL-OMON27857