Long term follow up of the clinical and immunological responses following HPV 16 E6/E7 synthetic long peptides vaccination in women with HPV 16 positive vulvar intraepithelial neoplasia grade 3

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To determine the long term clinical and immunological responses in patients with high grade VIN who have been vaccinated with an HPV 16 E6/E7 SLP vaccine approximately 3 years ago.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Reproductive neoplasms female malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON36101

Source
ToetsingOnline

Brief title
Long term follow up of HPV 16 E6/E7 SLP vaccine in VIN 3 lesions

Condition

- Reproductive neoplasms female malignant and unspecified

Synonym
VIN, vulvair intraepithelial neoplasia

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: HPV 16 E6/E7 SLP vaccin, Long term follow up, Therapeutic vaccination, VIN

Outcome measures

Primary outcome

The long term clinical and immunological responses will be assessed by use of history taking, histology, HPV typing and measurement of HPV-specific T-cell responses in peripheral blood T-lymphocytes. The immunological results will be compared with the results during the initial trial and the clinical results will be compared with the baseline and after 24 months of initial follow up characteristics.

Secondary outcome

Evaluation of adverse drug reactions in terms of local adverse events at the inoculation sites and possible related systemic events after HPV-SLP vaccination.

Study description

Background summary

Vulvar intraepithelial neoplasia (VIN) is a chronic disorder usually caused by high-risk human papilloma virus (hrHPV), most commonly HPV type 16.Spontaneous regression occurs in less than 1.5% of patients and the estimated risk of progression to malignant disease is 4% after treatment and 9% without treatment, while the recurrence rates are high with conventional treatments. A T-cell response plays a pivotal role in the clearance of an HPV infection. The early oncogene-encoded proteins E6 and E7 expressed in (pre)malignant HPV

lesions are the major targets for the immune system and consequently constitute the antigens for immunotherapeutic approaches to treat anogenital HPV lesions. A synthetic long overlapping peptide vaccine (SLP) against the HPV-16 oncogene-encoded E6 and E7 proteins (HPV16-SLP) was developed and several phase I/II studies have been performed to evaluate the safety and efficacy of this vaccine against HPV-16 associated anogenital disease.In a phase II clinical trial, in which 20 patients with HPV16 positive high-grade precancerous lesions (high grade vulvar intraepithelial neoplasia: VIN 3) were treated with HPV16-SLP, an objective clinical response rate of 79% and a complete and durable (>24 months) regression of the lesion in 47% of the patients was obtained. Notably, the clinical outcome was strongly correlated with the strength of the HPV16-specific T-cell associated IFN*-response as well as a relatively smaller size of the lesion at study entry. The group of patients with smaller lesions displayed stronger and broader vaccine-prompted HPV16-specific proliferative responses with higher IFNy ($P = 0.0003$) and IL-5 ($P < 0.0001$) levels than patients with large lesions. Characteristically, this response was accompanied by a distinct peak in cytokine levels after the first vaccination. In contrast, the patient group with larger lesions mounted higher frequencies of HPV16-specific CD4(+)CD25(+)Foxp3(+) T cells ($P = 0.005$) No severe side effects of the vaccination were reported though local side effects of the vaccination site such as swelling and discoloration of the skin were observed in the majority of vaccinated patients even in follow up. Histological examination of the vaccination sites, in some patients with local symptoms showed signs of granulomatous inflammation. In the current study we therefore aim to evaluate both the long term clinical and immunological response of this therapeutic vaccination as well as the adverse drug reactions.

Study objective

To determine the long term clinical and immunological responses in patients with high grade VIN who have been vaccinated with an HPV 16 E6/E7 SLP vaccine approximately 3 years ago.

Study design

A prospective cohort study

Study burden and risks

The burden and risks associated with participation in this follow up study are low since the interventions consist of considerably safe, venous bloodcollection and biopsies. A questionnaire will be sent and the patients will be asked to visit the outdoor patient clinic of the LUMC once. This visit will take approximately one hour where a gynaecological research as well as inspection of the inoculation sites will take place. Biopsies will be taken of the vulva (even in case of complete respons) and if present of the most

prominent vaccination site.
This follow up visit is of importance for a better understanding of the long term clinical and immunological respons after vaccination for further research and development of the therapeutic HPV 16 E6/E7 SLP vaccin for (pre)malignant anogenital diseases.

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

Patients are eligible and will be included if they participated in the initial phase II study and provide informed consent for the current study.

Exclusion criteria

There are no exclusion criteria for this follow up study.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-09-2011
Enrollment:	19
Type:	Actual

Ethics review

Approved WMO

Date:	12-07-2011
Application type:	First submission
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

No registrations found.

In other registers

Register	ID
CCMO	NL36676.058.11