A phase II study to determine the efficacy and safety of Vvax001, a therapeutic Semliki Forest Virus based cancer vaccine, in patients with HPV-16 induced grade 3 cervical intraepithelial neoplasia.

Published: 17-02-2020
Last updated: 10-04-2024

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Hepatobiliary neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON55191

Source
ToetsingOnline

Brief title
Vvax001 cancer vaccine in HPV-16 related disease.

Condition

- Hepatobiliary neoplasms malignant and unspecified
- Reproductive neoplasms female malignant and unspecified

Synonym
cervical neoplasia / cervical cancer

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: KWF subsidie

Intervention

Keyword: cervical neoplasia, HPV-16, phase II, therapeutic immunization

Outcome measures

Primary outcome

Primary study endpoint is clinical efficacy of Vvax001. To assess vaccine induced clinical responses, histology of the pre-treatment diagnostic biopsy will be compared to histology of the post- treatment therapeutic biopsy/LLETZ. A positive response is defined as a reduction from CIN3 to CIN1, or a change from CIN3 to no dysplasia.

Secondary outcome

Secondary endpoints are 1) the immunological activity of Vvax001 by monitoring HPV-16 E6,7-specific T-cell immune responses in peripheral blood at baseline, week 7, week 9, week 17 and week 25; 2) HPV16 clearance; and 3) potential side effects/adverse events related to Vvax001.

Study description

Background summary

Human papillomavirus (HPV) infection is an important cause of premalignant genital and oropharyngeal lesions, cervical cancer, vulvar, anal, and penile cancer. HPV-induced cancer is the second largest cause of cancer deaths in women worldwide. Current treatment for premalignant HPV-induced genital lesions primarily relies on surgery, which can be discomforting and carries a risk of complications like bleeding, cervical stenosis and/or incompetence which may lead to infertility and partus prematuris/immaturis. Above all, it does not

necessarily eradicate the underlying HPV infection completely. Therapeutic immunization is a very attractive alternative to the current treatment options for precancerous lesions and (invasive) cancer. The immune cells induced by cancer immunotherapy can target the tumor cells and kill them. When long-lasting immunity is induced the immunotherapy may prevent recurrence of the disease. Therefore, the approach taken in this study is to immunize with a replication-incompetent Semliki Forest Virus (SFV) vector encoding HPV-derived tumor antigens. Intramuscular immunization with these replication-incompetent SFV particles (Vvax001) is aimed at eliciting a therapeutic anti-tumor response.
A phase I study has been conducted in which vaccination with Vvax001 induced HPV16-E6,7-specific immune responses in women previously treated for cervical intraepithelial neoplasia (CIN) or cervical cancer (CC). Intramuscular immunization with Vvax001 was well tolerated, showing only mild to moderate local adverse reactions. Altogether, the data of this study justify testing of Vvax001 in CIN grade 3 (CIN3) patients in this phase II study.

Study objective

The primary objective of this trial is to determine clinical efficacy of Vvax001 in CIN3 patients.

Study design

HPV16-positive CIN3 patients will receive three bilateral intramuscular immunizations of Vvax001 (total concentration 5x10e7 infectious particles [IP]) with an interval of 3 weeks between vaccinations. Patients will be monitored for regression of CIN3 lesions by colposcopy and digital imaging at week 9, week 17 and week 25. When complete regression of the CIN3 lesion is observed, a biopsy will be taken in week 25 to confirm regression. If complete regression has not occurred by 25 weeks, a standard-of-care surgical treatment (LLETZ) will be performed. If progression of the CIN3 lesion is observed during the 25 week interval, a biopsy will be taken to confirm pathological progression. If pathological progression has occurred, patients will immediately undergo a LLETZ. If no pathological progression has occurred, patients will continue to be monitored by colposcopy. Patients with a complete regression will be followed-up by cytology at 3, 6 and 12 months after exit from the study. Hereafter, patients will be monitored through regular national screening programs.

Intervention

Patients will receive three immunizations, with an interval of 3 weeks between each immunization. Each vaccination will be given as two injections; 1 injection in each leg. The injections will be administered intramuscularly in the upper legs, preferably in the m. vastus lateralis. Patient evaluation will

be performed before immunization and during the first follow-up visit (week 7) including history, physical examination, full blood count, urea, electrolytes and liver function tests. Besides, a pregnancy test will be taken before each vaccination. Participants may directly leave the study site after injection of Vvax001. Participants will be contacted by telephone 4-8 hours after immunization to obviate any adverse events (AE's). Peripheral blood mononuclear cells (PBMC) will be collected at baseline, first follow-up visit (week 7), colposcopy (week 9 and week 17) and at time of biopsy (week 25) to monitor HPV-specific immune responses. Colposcopy and digital imaging will be performed after immunization in week 9, in week 17 and in week 25 to monitor regression of the CIN lesions. If full regression of the lesion does not occur, LLETZ will be performed 25 weeks after the first immunization. LLETZ will also be performed if progression occurs (proven by biopsy) during the study. When complete regression of the CIN3 lesion is observed by colposcopy, a biopsy will be taken in week 25 to confirm regression. In this case, no LLETZ will be performed. The biopsies and surgical specimens will be used to determine vaccine-induced pathological responses.

Study burden and risks

The study procedures require 8 visits to the hospital. Vaccination by bilateral intramuscular injection is performed three times. Standard-of-care LLETZ treatment will be postponed by a maximum of 25 weeks. We consider the risks associated with this delay very minimal since patients will be closely monitored during the time of the trial. Standard-of-care colposcopies will be performed (two in total; one at diagnosis [week 0] and one at time of LLETZ [week 25]). Patients will undergo an additional 2 colposcopies during the trial period for monitoring regression of CIN3 lesions (week 9 and week 17). 8 venapunctions will be performed for PBMC and/or biochemistry. Toxicity will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Given the results of the Phase I clinical study, and previous clinical experience with similar viral vector vaccines, only mild to moderate injection site reactions are anticipated from administration of Vvax001.

Potential benefit for the patients is vaccine-mediated regression of the CIN3 lesion and HPV16 clearance, due to the induction of a long-lasting protective HPV16-specific immune response. Hereby, the invasive LLETZ procedure and recurrence of the disease can be prevented.

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

Adult female patients (>=18 years) who have newly been diagnosed with HPV-16 positive CIN3 lesions and have signed written informed consent according to local guidelines. Patients of child-bearing potential should test negative using a pregnancy test and agree to utilize effective contraception during the entire treatment and follow-up period of the study.

Exclusion criteria

* PAP5 lesions.
* Previously undergone treatment for CIN lesions.
* Adenocarcinoma in situ within CIN3 lesion
* History of autoimmune disease or other systemic intercurrent disease that might affect the immunocompetence of the patient, or current or prior use (4 weeks before start of the study) of high dose immunosuppressive therapy.
* History of a malignancy except curatively treated low-stage tumors with a histology that can be differentiated from the cervical cancer type.
* Participation in a study with another investigational drug within 30 days

prior to the enrolment in this study.
* Clinically significant findings as judged by the investigator on screening/study entry including those from biochemistry, haematology and urinalysis performed at screening.
* Any condition that in the opinion of the investigator could interfere with the conduct of the study.
* Pregnancy.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	23-03-2021
Enrollment:	18
Type:	Actual

Ethics review

Approved WMO Date:	17-02-2020
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	30-03-2020
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	22-06-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-06-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-12-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-01-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-03-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-03-2021
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	EUCTR2019-004050-29-NL
CCMO	NL71783.000.19