Therapeutic Vaccination against Human Papillomavirus Type 16 for the Treatment of Anal Intraepithelial Neoplasia in HIV+ Men

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The objective of the current proposal is to assess, in a phase 1/2 study, the safety and efficacy of this synthetic vaccine SLP-HPV-01® in HIV+ men with CD4 counts > 350 x 10E6/l and intra-anal high-grade, HPV16 positive AIN, who failed on...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Viral infectious disorders
Study type	Interventional

Summary

ID

NL-OMON41467

Source
ToetsingOnline

Brief title
Therapeutic HPV-16 Vaccination for the Treatment of Anal Dysplasia.

Condition

- Viral infectious disorders
- Gastrointestinal neoplasms malignant and unspecified

Synonym
anal intraepithelial neoplasia

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: ZON MW Translationeel Onderzoek,ISA Pharmaceuticals Leiden.

Intervention

Keyword: anal neoplasia, hiv, HPV, human papillomavirus

Outcome measures

Primary outcome

The primary clinical end points will be both toxicity/ safety, and the regression of the lesions at 3,6 and 12 months, as assessed by HRA, with biopsies taken of the lesion sites.

Secondary outcome

Secondary endpoints are regression of lesions at 18 months and HPV16-specific immunity in blood will be measured: i.e. ELISPOT (IFNg) for ex-vivo detection of antigen-specific responses and multiparametric intracellular cytokine/extracellular activation marker staining to determine the type (CD4+ and/or CD8+) and function (activation status and/or cytokines) of T-cells that respond.

Study description

Background summary

Since the introduction of combination antiretroviral therapy (cART), human immunodeficiency virus (HIV)-related morbidity and mortality have considerably decreased. However, as a result of the significantly prolonged life span of HIV-positive patients, new causes of morbidity and mortality have become evident. In particular, anal cancer incidence has increased dramatically in HIV-positive men. Like cervical cancer, anal cancer is causally linked to

infections with high-risk papillomaviruses (HPV), and is preceded by cancer precursor lesions: anal intraepithelial neoplasia (AIN). Over 90% of HIV-positive MSM have persisting anal HPV infection, in 88% of patients high-risk HPV is present, and high-grade disease (AIN 2 or 3, HG AIN) is present in 25-52% of all HIV+ MSM. The majority of HG AIN is caused by HPV type 16. As in cervical intraepithelial neoplasia, early diagnosis and treatment of AIN have been advocated to prevent malignancy.

Several treatment options exist for AIN, but success rates are disappointingly low. An alternative strategy might be therapeutic HPV vaccination. In women with vulvar intraepithelial neoplasia (VIN), a condition with a comparable pathogenesis, therapeutic vaccination with a synthetic long-peptide vaccine SLP-HPV-01® , consisting of a mix of long peptides from the HPV-16 viral oncoproteins E6 and E7, was well tolerated, and proved to be effective in a high percentage of women, with a durable response, and induction of HPV-16-specific immunity.

Study objective

The objective of the current proposal is to assess, in a phase 1/2 study, the safety and efficacy of this synthetic vaccine SLP-HPV-01® in HIV+ men with CD4 counts > 350 x 10E6/l and intra-anal high-grade, HPV16 positive AIN, who failed on previous treatment.

Study design

The first phase of the study is a dose-response study, with 4 different dosage schedules (1,5,10; 5,10,20; 10,20,40; and 40,40,40,40 µg of SLP-HPV-01®, administered intradermally with a three-week interval), each dosage schedule with or without the co-administration of pegylated interferon-α (Pegintron 1 µg/kg s.c.) at the day of vaccine administration. Each vaccination schedule is to be tested in 5 patients.
The vaccination schedule that induces in HIV-positive MSM the best HPV16-specific response compared to that of the women with VIN in our previous study, is considered the optimal schedule. The size of this dose group will be increased to a total of 20 patients by treating an additional 15 patients.

Intervention

Patients will be vaccinated 3 or 4 times with a 3-week interval with the SLP-HPV-01® vaccine.
High-resolution anoscopy (HRA) will be performed at inclusion, and repeated at 3, 6,12 and 18 months. The transformation zone will be photographed at each visit. Detailed photos plus biopsies of lesion sites will be obtained. From venous blood samples PBMCs will be obtained before the first (pre), 3 weeks after the first (post-1), 3 weeks after the second vaccination (post-2), 3

weeks after the third vaccination (post-3) as well as 3 weeks after the 4th vaccination (post-4).

Study burden and risks

During the course of the study high-resolution anoscopy (HRA) will be performed five times, in total 545 ml blood will be drawn, and the patient has to visit the AMC in total 12 times during the 18 months of the study. Potential risks are the possible side effects of the vaccine and the Pegintron injections. This is justified by the fact that the vaccine was tolerated well during a previous study in women with vulvar neoplasia, and therapy is intended to be therapeutic for their therapy-resistant high-grade anal intra-epithelial neoplasia, which is a very prevalent condition among HIV+ men who have sex with men.

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

• HIV+, CD4 count > 350/ul,
• Biopsy-proven intra-anal high-grade AIN caused by HPV16, resistant to, or recurring after previous treatment with cauterization, 5FU or imiquimod. A patient is considered resistant to cauterization if after 2 cauterization sessions still lesions are found. A patient is considered resistant to 5FU or imiquimod if after 4 months of weekly (multiple day) application still lesions are found.
• Good performance status (a Karnofsky performance score of >=60 [on a scale of 0 to 100, with higher scores indicating better performance status])
• Normal pretreatment laboratory blood values as described previously

Exclusion criteria

• Immunosuppressive medication or other diseases associated with immunodeficiency
• Life expectancy < 1 year
• History of anal carcinoma
• IFN-α criteria (see SmPC): severe cardiac, thyroid, hepatic or central nervous system disease, including severe depression in the past.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-08-2013
Enrollment:	55
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	PegIntron
Generic name:	peginterferon alfa-2b
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	19-04-2013
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-05-2013
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-09-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-02-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-02-2016
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	EUCTR2012-005466-34-NL
CCMO	NL42802.000.12