Randomised Controlled Study on the Effects of Imiquimod, a TLR 7 Activating Agent, on the HPV16-Specific Immune Response Following HPV16 E6/E7 Synthetic Long Peptides Vaccination in Women with HPV16 Positive High Grade Vulvar/Vaginal Intraepithelial Neoplasia.

Published: 17-03-2008
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Primary objective:To compare the immunological response to vaccination with HPV16 E6 and E7 synthetic long peptides with concomitant application of imiquimod at the vaccination site with vaccination without the concomitant application of imiquimod....

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Reproductive and genitourinary neoplasms gender unspecified NEC
Study type	Interventional

Summary

ID

NL-OMON35679

Source
ToetsingOnline

Brief title
HPV16 E6/E7 SLP vaccine and Imiquimod in High Grade VIN/VaIN

Condition

- Reproductive and genitourinary neoplasms gender unspecified NEC

Synonym
Morbus Bowen, vulvar and vaginal intraepithelial neoplasia

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: ISA Pharmaceuticals

Intervention

Keyword: HPV, imiquimod, vaccination, VIN/VaIN

Outcome measures

Primary outcome

The primary end point is the evaluation of the systemic immunological response.

The following criteria will be used for this evaluation:

- proportion of patients developing a directly ex-vivo detectable CD8+ T-cell

response after 4 vaccinations

Aldara Subprotocol Amendment 1, 19 April 2010:

Descriptive statistics will be used to quantify the (change in) parameters

measured.

Secondary outcome

Secondary study endpoint:

Safety will be assessed during the whole study by collecting all adverse events

(with a focus on administration site reactions), vital signs, blood-chemistry

and haematological parameters will be assessed at baseline, before the third

vaccination, and 3 weeks after the last vaccination. Immunological parameters

tested as secondary endpoints will be proliferation, cytokine production and

protein recognition by circulating and vaccine-site- or lesion-homing

HPV16-specific T-cells.

Clinical response will be assessed three months and 12 months after the last vaccination. For the evaluation of response, lesions will be described and measured bi-dimensionally, by the same qualified investigator. Furthermore monitoring of the lesions by digital photography will take place.

Aldara Subprotocol Amendment 1, 19 April 2010:

Not applicable

Study description

Background summary

Human Papilloma Virus (HPV)16 infection may cause a chronic disorder in the epithelial layers of the vulva known as vulvar intraepithelial neoplasia (VIN), and vagina (vaginal intraepithelial neoplasia, VaIN). 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. Vaccination with HPV16 E6 and E7 long peptides is known to induce a systemic HPV16-specific type 1 (IFN gamma) and type 2 (IL-5) CD4+ T-cell response that seems suited to overcome these deficits. However, the CD8+ T-cell response was weak and only detectable after in vitro stimulation. In order to improve the magnitude of the CD8+ T cell response the application of imiquimod (a TLR7 ligand) to the vaccination site may be beneficial. In addition this may enhance the homing of both CD4+ and CD8+ HPV-16 specific T-cells to the disease site.

Aldara Subprotocol Amendment 1, 19 April 2010:
The analysis of a Serious Adverse event in the HPV01/01 study, where a young woman died of an acute myocardial infarction shortly after receiving the second vaccination, resulted in a discussion whether the vaccine could have initiated that event. The patient appeared to have severe coronary atherosclerosis, which probably was a sufficient explanation of the event. However, since it is known that inflammatory mediators (cytokines) are able to induce coagulation activation, the event triggered the need to assess whether this is the case with the HPV16 E6/E7 SLP vaccine. Markers for coagulation activation will therefore also be measured in this study
Purpose will be to improve the knowledge on the potential adverse effects of

this vaccine, in order to better assess the risks for future clinical trials.

Study objective

Primary objective:
To compare the immunological response to vaccination with HPV16 E6 and E7 synthetic long peptides with concomitant application of imiquimod at the vaccination site with vaccination without the concomitant application of imiquimod.

Secondary objectives:
To compare the safety and clinical response to vaccination with HPV16 E6 and E7 synthetic long peptides with concomitant application of imiquimod at the vaccination site with the response to vaccination without the concomitant application of imiquimod.

Aldara Subprotocol Amendment 1, 19 April 2010:
The primary objectives of this study are:
• To assess the acute inflammatory response after vaccination with HPV16 E6/E7 SLP vaccine
• To assess whether the acute inflammatory response after vaccination with HPV16 E6/E7 SLP vaccine induces coagulation activation

Study design

This is a randomised, controlled, parallel group phase I/II study

Aldara Subprotocol Amendment 1, 19 April 2010:
An exploratory analysis in ongoing Phase 2 study

Intervention

The vaccine consists of HPV16 E6 and E7 synthetic long peptides (ISA-HPV-01) in DMSO / 20 mM PBS / Montanide ISA 51 20/30/50 v/v/v. Dosing is 300 µg /peptide, in 2 separated subcutaneous injections, containing seven E6 peptides and two E6 together with all four E7 peptides.
All patients will be vaccinated four times at three weeks intervals.

Patients will be randomized to one of two arms: arm 1 is to receive local application of imiquimod on the vaccination sites one hour and 48 hours after each vaccination, arm 2 will not apply anything to the vaccination site.

Aldara Subprotocol Amendment 1, 19 April 2010:
Patients will not receive any treatment as part of this study.

Study burden and risks

The amount of visits is 9, during a period of approximately 14 months. At 4 visits the vaccination is performed at the upper right and left arm or upper right and left leg (2 vaccinations at a time) and an intravenous line is placed. At the screening visit and the vaccination visits (before, 15 minutes, 1 hour and 4 hour after the vaccination) pulse, blood pressure, respiratory rate and body temperature are measured. Special attention is paid to symptoms that may indicate an allergic reaction (15 min, 1 hour and 4 hour)
After 1 hour and 48 hours after the vaccination imiquimod is applied on the vaccination site.
The following procedures are performed: 4 blood draws (with a total volume of 400 ml), 5 times a pregnancy test, 6 times physical examination, 3 times a biopsy of the VIN/VaIN lesion, 1 x a biopsy of both last vaccination sites, 3 times control of the VIN/VaIN lesion.
The results of other clinical trials with the vaccine show that in most patients the vaccine was safe.Redness and swelling of the skin after vaccination often occurs. Vaccinations were associated with fever and flu-like symptoms for a short period.
In some patients shortly after the vaccination an allergic reaction occurred with itching, swelling of the eyelids/lips and in one case difficulty in breathing. The allergic reaction can be treated well with medication. The swelling/discoloration of the skin at the vaccination sites may persist for weeks to months, and possibly even longer, up to years after vaccination. In some cases a painful swelling of the skin occurred together with symptoms of infection.
Imiquimod is generally well tolerated. Known side effects are reactions of the skin at the place where the cream is applied, flu-like symptoms, headache and muscle pain. Because imiquimod is only used in a small dosage, we do not expect a lot of side effects.
The research is group-related.

Aldara Subprotocol Amendment 1, 19 April 2010:
There are 2 extra visits for the subprotocol.
After the first and the second vaccination there is 1 extra measurement for vital signs: 24 hours after vaccination. Furthermore there are extra blood draws before vaccination, 4 hours after vaccination and 24 hours after vaccination. In total 6 x 5 mL blood is drawn (with a total of 30 ml extra).
For the visit 24 hours after the vaccinations an extra visit to the hospital is necessary.

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 of 18 years and older
- willing and able to comply with the protocol and to provide informed consent in accordance with institutional and regulatory guidelines
- histological evidence of high grade usual VIN/VaIN, HPV16 positive
- baseline laboratory findings; white blood cells (WBC) > 3,000 x 109/l, lymphocytes > 1,000 x 109/l, platelets > 100 x 109/l, HIV- and HBV-negative
- patients of child-bearing potential should test negative using a serum pregnancy test and agree to utilize effective contraception during the entire treatment and follow-up period of the study

Exclusion criteria

- known hypersensitivity to the vaccine or imiquimod or to any of the respective excipients.
- indication of a current active infectious disease of the vulva or other infections that need

medical attention, other than HPV16
-VaIN lesions that are not distinguishable from a co-existing cervical intraepithelial neoplasia (CIN) lesion
- history of an autoimmune disease or other systemic intercurrent disease that might affect the immunocompetence of the patient, or patients receiving immunosuppressive therapy including transplant recipients
- history of a second malignancy except curatively treated low-stage tumours with a histology that can be differentiated from the vulvar/cervical cancer type
- radiotherapy, chemotherapy administered within 4 weeks prior to the enrolment visit
- participation in a study with another investigational drug within 30 days prior to the enrolment in this study
- Any condition that in the opinion of the investigator could interfere with the conduct of the study

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-10-2008
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Aldara
Generic name:	imiquimod

Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	HPV16 E6/E7 synthetic long peptides vaccine

Ethics review

Approved WMO Date:	17-03-2008
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-04-2008
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-11-2008
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-10-2009
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-11-2009
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-03-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	11-05-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-10-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-10-2010
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	EUCTR2007-005230-37-NL
CCMO	NL21215.000.08