Clinical and immunological effects of imiquimod and HPV-vaccination compared to imiquimod alone in female patients with Usual type VIN: proof of principle.

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Primary objectives: (1) Evaluation of the efficacy of vaccination against HPV 16, 18, 6 and 11 followed by local applications of imiquimod 5% cream compared to treatment with imiquimod alone for usual type VIN, (2) evaluation of the systemic and...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Viral infectious disorders
Study type	Interventional

Summary

ID

NL-OMON33950

Source
ToetsingOnline

Brief title
Effects of HPV-vaccination and imiquimod in Usual type VIN

Condition

- Viral infectious disorders
- Reproductive and genitourinary neoplasms gender unspecified NEC
- Skin and subcutaneous tissue disorders

Synonym
precancerous lesion of the vulvae, Vulvar Intraepithelial neoplasia

Research involving

Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W,Sanofi Pasteur

Intervention

Keyword: gardasil, high risk HPV, imiquimod, VIN

Outcome measures

Primary outcome

Clinical response to the treatment in VIN lesions after the end of imiquimod treatment and the last vaccination, measured by 1) reduction in lesion size, 2) histological regression of usual type VIN to *normal* vulvar tissue and 3) relieve of symptoms. Other main study parameters are absence of HPV DNA in the original VIN lesions after treatment, normalization of immunocompetent cell counts and production of cytokines in peripheral blood and by Peripheral Blood Mononuclear Cells (PBMCs).

Secondary outcome

Secondary study parameters include 1 presence of antibody titres against HPV 16,18, 6, and 11.

Study description

Background summary

Usual type Vulvar Intraepithelial Neoplasia (VIN) is a premalignant disorder caused by a persistent HPV-infection that needs to be treated proactively. Recently our group reported in the New England Journal of Medicine on a randomized clinical trial (RCT) in which we successfully used a non-invasive new treatment for usual type VIN. It was observed that imiquimod treatment

resulted in a complete response in 35% of patients and represented a significant reduction in lesion size for an additional 46% of patients. Furthermore, after treatment with imiquimod, HPV virus could no longer be detected at the site of the lesion in 58% of patients. On the basis of these findings we recommend to use imiquimod as a first-line treatment for VIN. In the current proposal we are seeking to further improve imiquimod treatment by combining it with a vaccination against HPV. The rationale behind this approach is that this way we will be boosting different aspects of cellular immunity: imiquimod binds TLR7 and 8, activates dendritic cells to produce cytokines thus evoking an influx of immunocompetent cells in the treated area, while vaccination induces a systemic cellular response by activating dendritic cells to present antigen to naïve T-lymphocytes, thus activating them. This way we will enhance cellular immunity and will consequently further enhance disease clearance in patients suffering from VIN.

Study objective

Primary objectives: (1) Evaluation of the efficacy of vaccination against HPV 16, 18, 6 and 11 followed by local applications of imiquimod 5% cream compared to treatment with imiquimod alone for usual type VIN, (2) evaluation of the systemic and local immune response to both treatments, and (3) evaluation of the effect of treatments on HPV DNA presence in VIN lesions.
Secondary objectives: Evaluation of the effect of vaccination against HPV types 16,18, 6 and 11.

Study design

This study is designed as a randomized, placebo-controlled, double-blinded proof of principle study.

Intervention

Included patients will be double-blinded and randomized to receive 5% imiquimod cream + HPV-vaccination or 5% imiquimod cream with placebo vaccination (saline). Vaccination will take place in three dosages at weeks 0, 8 and 24. Imiquimod will be applied to the site of the lesion twice weekly for a period of 16 weeks (weeks 8-24). Clinical assessment will take place every 4 weeks during treatment and 7 months after start of imiquimod treatment.

Study burden and risks

Risk and burden are linked to protocol procedures, such as injection of the vaccine, blood withdrawal and biopsy sampling. Although these are routine procedures, carried out by medical qualified personnel, they may cause side effects or discomfort to the subject. However, it is expected that these procedures will generally be well tolerated.

Gardasil® or placebo injection will be given three times; known side effects from Gardasil® are local reactions at the injection site (e.g. pain, redness, bruising, itch) and general reactions as fatigue, nausea and fever. Most side effects are transient and considered mild. Rare complications are the development of urticaria and bronchospasm (<0.01%).
Imiquimod will be applied twice weekly for 16 weeks; known local side effects are erythema, ulceration, vesiculation, excoriation, and discharge, and are readily reversible with discontinuation of dosing.

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

- Histological proven usual type VIN, without invasion
- Previous treatment with imiquimod for 12-16 weeks with a partial response to

imiquimod treatment defined as a reduction in lesion size of 26%-99%
- The patient is willing to use a medically acceptable method of contraception throughout the study
- Age 18 and above

Exclusion criteria

- (Micro-)invasive carcinoma
- Pregnancy and/or breastfeeding
- Past history of vulvar cancer
- Differentiated (non HPV-related) VIN
- Other treatment of VIN or anogenital warts within 1 month of start trial
- Hypersensitivity to any components of the vaccine or cream formulation
- History of psoriasis or other inflammatory dermatosis of the vulva
- Immunodeficiency (e.g. HIV, corticosteroid use)
- Insufficient understanding of the Dutch Language
- Partial responders who are disease-free at study-entry due to other treatment of VIN

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	98
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	AldaraTM cream, 5%
Generic name:	Imiquimod
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	23-03-2009
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-09-2009
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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2008-008251-42-NL
CCMO	NL26014.000.09