Phase I study: to determine the biological activity of two HPV16 E6 specific peptides coupled to Amplivant®, a Toll-like receptor ligand in nonmetastatic patients treated for HPV16-positive head and neck cancer

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Primary objective: to determine the biological activityof Hespecta that is able to induce HPV16 E6-specific T-cell immunity within a proposed dose escalation of 1, 5, 20 or 50 µg/peptide - conjugate in patients treated for HPV16+ OSCC.Secondary...

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

Summary

ID

NL-OMON41192

Source
ToetsingOnline

Brief title
Phase I Study: Hespecta vaccination in HPV+ head and neck cancer

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
oropharyngeal squamous cell cancer; head and neck cancer

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: ISA pharmaceuticals,KWF;TI Pharma;ISA Pharmaceuticals

Intervention

Keyword: Cancer, HPV, Immunotherapy, Vaccination

Outcome measures

Primary outcome

Primary objective is to determine the biological activity of Hespecta that is able to induce HPV16 E6-specific T-cell mediated immunity within a proposed dose escalation of 1, 5, 20 or 50 µg/peptide-conjugate in patients treated for HPV16+ OSCC. Blood samples will be drawn and used in an array of complementary immunological assays (HPV16-specific proliferation assay, IFNγ-ELISPOT, cytokine bead array and multiparameter flow cytometry analysis) to assess the biological activity of Hespecta. These established assays are performed at 4 different time points (baseline and 3 time points after start of vaccination). Vaccine-induced immunity in the different assays is defined as a post-vaccination response that is at least 3 times higher than the pre-vaccination response. Biological activity is identified if it is seen in at least 2 assays at 2 consecutive follow-up time points after the baseline assessment, in line with CVCTWG criteria.

Secondary outcome

Secondary objectives: to study safety of Hespecta by collecting all adverse

events according to CTCAE v4.0

Study description

Background summary

Human papillomavirus (HPV) has been found to be associated with several types of cancer, amongst others oropharyngeal squamous cell cancers (OSCC). The number of HPV attributable OSCC is strongly increasing, and comprises a large proportion of this disease in young adults and women. HPV16 is the far most common HPV type detected. HPV16 encodes the two tumor-specific oncoproteins E6 and E7. In most humans the virus is cleared. However, in some individuals, infection results in an uncontrolled persistent HPV16 infection that due to expression of the viral oncoproteins E6 and E7 may lead to the formation of malignancies. Moreover, these oncoproteins maintain the malignant state of the transformed cells. The virus-specific interferon-γ (IFNγ)-producing CD4+ helper T cells (Th1 cells) and CD8+ cytotoxic T-lymphocytes (CTL) are able to recognize peptides processed from the highly immunogenic E6 and play a critical role in the elimination and/or control of the virus. Studies in patients with HPV associated tumors (such as OSCC) showed that the spontaneous HPV-specific T-cell responses, are weak and fail to sufficiently control tumor outgrowth. Preexisting T-cell responses specific against E6 and E7 in patients with HPV related tumors such as OSCC are associated with better outcome after treatment. Since the HPV16-transformed tumor cells constitutively express the two HPV16 encoded E6 and E7 oncoproteins, these viral antigens are considered to be excellent targets for immunotherapeutic vaccine strategies aiming at reinforcing the tumor-specific T-cell response. Previous vaccination studies showed that the use of our first generation HPV16 synthetic long peptides vaccine (HPV16-SLP) was safe and highly immunogenic in patients with HPV-induced anogenital lesions. Vaccination of patients with cervical cancer (CxCa) also resulted in the induction of HPV16-specific T-cell responses but the nature and strength of the induced T-cell responses was not sufficient for the regression of these tumors. Specifically, it was concluded that the polarization of the T-cell response to Th1 (IFN*-response) was not optimal and a much stronger CD8+ T-cell response was required for clinical efficacy. These results initiated the development of new HPV16 vaccination strategies that are able to polarize the induced Th1 response and obtain strong CD8+ T-cell cytotoxicity. One of these developments consists of conjugating two of the HPV16 E6 SLP to Amplivant®, a synthetic Toll-like receptor (TLR) 2 ligand. These two peptides cover the most immunodominant regions of the overlapping HPV16-SLP set and contain both Th and CTL epitopes. Peptide conjugated Amplivant® has been selected because it is acknowledged for its capacity to strongly enhance antigen presentation by dendritic cells (DCs), enhance T-cell priming and cause superior induction of effective anti-tumor CTL responses in

mouse tumor models, compared to a mixture of free TLR ligand and peptide. In preclinical murine studies, Amplivant®-conjugated SLP showed 10 to 100 times higher bioactivity compared to unconjugated SLP, in terms of induced immune responses. In addition, the quantity and quality of human T-cell responses, and especially the HPV16-specific CD8+ T-cell response, in cancer patients could be markedly enhanced by ex vivo stimulation with Amplivant®-conjugated SLPs. Here we propose a phase I study to establish the biological activity using this highly promising novel therapeutic vaccine concept named: Hespecta (HPV E Six Peptide Conjugated To Amplivant®), to induce HPV16 E6-specific T-cell responses.

Study objective

Primary objective: to determine the biological activityof Hespecta that is able to induce HPV16 E6-specific T-cell immunity within a proposed dose escalation of 1, 5, 20 or 50 µg/peptide - conjugate in patients treated for HPV16+ OSCC. Secondary objectives: to study safety of Hespecta by collecting all adverse events according to Common Terminology Criteria for Adverse Events v4.0 (CTCAE).

Study design

This is a single center, translational dose escalation phase I trial.

Intervention

Patients first treated with curative intent for advanced HPV16+ OSCC will be vaccinated intradermally (i.d.) in four dose escalation groups (1, 5, 20 or 50 µg/peptide). Each dose group exists of 6 patients. The dose range is based on a 10-100 fold higher bioactivity of Amplivant® conjugated peptides in preclinical studies. The starting dose of this dose escalation trial is based on preclinical murine experiments showing that a dose of 1 µg per Amplivant® conjugated peptide resulted in no severe toxicity and a suboptimal immune response in that the magnitude of the immune response increased when mice were given a higher dose of vaccine. We reason that this provides the best scientific basis for the first dose to start with. As Amplivant® conjugated peptides are expected to induce T-cell responses more effectively compared to unconjugated peptides, the lowest dose known (50 µg per peptide) of unconjugated peptides able to induce T-cell responses is used as highest dose in this trial. From this starting dose an ascending dose range is proposed, evaluating four doses (1, 5, 20, 50 micrograms per peptide). Notably, the higher the dose the smaller the dose-fold increase between the doses (5, 4, 2.5 times), this should allow for maximal safety. Patients will be vaccinated three times with an interval of three weeks with a fixed dose of Hespecta (i.e. no escalating dose within the patient). Vaccination will start with the i.d. injection of the lowest dose. The decision to start enrollment at the next dose

level will be made by the Independent Data Monitoring Committee (IDMC), and will be based only on the assessment of safety data when 4 out of 6 patients have completed the first follow up visit after the third vaccination. If in two or more patients, grade 3 or 4 vaccine related toxicity occurs the dose escalation phase will be discontinued. If in the lowest dose group two patients experience grade 3 or 4 vaccine related toxicity, there is no safe dose and the study will be discontinued.

Study burden and risks

Patients will visit the clinic during the trial seven additional times (screening visit, three vaccination visits, and three follow up visits).These follow up visits are combined with regular treatment follow up visits. Potential risks with the current trial are mainly linked to the toxicity related to the treatment compounds utilized in Hespecta. Although the rabbit toxicity testing of Hespecta (see IMPD brochure) did not show any severe side effects, it is expected from previous results with HPV16-SLP, that the most important AEs of Hespecta may consist of fever, chills, nausea, malaise, fatigue and local reactions at the vaccination site including pain, redness, swelling and itching. Generally the AEs after vaccination with HPV16-SLP did not exceed grade 2 according to the CTCAE criteria. Almost all patients, vaccinated with HPV16-SLP formulated in Montanide ISA51 experienced local injection site reactions (grade 2). After vaccination, ulceration/abscess formation occasionally occurred, estimated to be in between 1 and 5% of vaccinations, due to the use of this Montanide as adjuvant. The current vaccine is administered without Montanide, and therefore, it is expected that these local reaction will be less severe. Allergic reactions have occurred in a few patients after HPV16-SLP vaccinations, controlled with antihistamines. Vaccinations should therefore only be administered in a clinic where immediate treatment of severe allergic reactions is possible. Thus, after vaccinations, patients will be closely monitored during one hour after injection to provide means for immediate treatment of allergic reactions. In addition to the standard of care, the patients participating in the trial will receive three vaccinations with Hespecta for the induction of a strong and broad CTL response against HPV16 E6. Study patients will not be paid for their participation however any study-related travel expenses will be reimbursed.

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 must meet all the following criteria in order to be included in the study:
1. Histologically documented evidence of HPV16 positive stage III or IV OSCC treated with curative intent
2. No evidence of residual OSCC based on physical examination at the completion of curative intent therapy
3. At least four weeks and less than twelve weeks after last anti-tumor treatment
4. Willing and able to comply with the protocol and to provide informed consent in accordance with institutional and regulatory guidelines
5. Patients must be 18 years or older.
6. 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 (up to 2 months after the last vaccination)
7. Patients must be in good general health and ambulatory, with an ECOG performance status of 0 or 1

Exclusion criteria

Patients who meet the following exclusion criteria will not be eligible for admission to the study:

1. Radiotherapy, chemotherapy or other potentially immunosuppressive therapy administered within 4 weeks prior to the enrolment visit
2. History of an autoimmune disease or other systemic intercurrent disease that might affect the immunocompetence of the patient, or patients receiving immunosuppressive therapy, except for topical application
3. History of a second malignancy except curatively treated low-stage tumors with a histology that can be differentiated from OSCC
4. Receipt of another investigational product within the previous 4 weeks or at any time during the study period.
5. Receipt of prior HPV directed immunotherapy
6. Hematology and biochemistry:
• Absolute Neutrophil Count (ANC) < 1.5 x 109/L, or platelet count < 100 x 109/L or hemoglobin < 6 mmol/L.
• Serum (total) bilirubin > 2 x upper normal limit (ULN);
• Aspartate Aminotransferase (ASAT) or Alanine Aminotransferase (ALAT) > 2.5 x ULN;
• Alkaline phosphatase levels > 2.5 x ULN;
• Serum creatinine within normal limits or calculated clearance >= 50 mL/min/1.73 m2 for patients with serum creatinine levels above the institutional normal value
7. Active HIV, chronic hepatitis B or C infection.
8. Any condition that in the opinion of the investigator could interfere with the conduct of the study

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-01-2016
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Hespecta

Ethics review

Approved WMO Date:	11-04-2014
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-10-2014
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-09-2016
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	EUCTR2014-000658-12-NL
CCMO	NL48274.000.14