Een fase I/II vaccinatie studie met patient eigen dendritische cellen geladen met TAT, REV en NEF mRNA in HIV geïnfecteerden tijdens stabiele HAART.

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Ethische beoordeling	Positief advies
Status	Werving gestopt
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON25488

Bron
NTR

Verkorte titel
DC-TRN

Aandoening

HIV-1 infection, seroposoitive anti-retroviral treatment, cellular immunity, early proteins, Tat, Rev, Nef

Ondersteuning

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Overige ondersteuning: initiator

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

To determine safety and toxicity of the subcutaneous and intradermal (SC/ID) administration of autologous dendritic cells (DC) electroporated with mRNA encoding Tat, Rev and Nef in HIV-1 infected patients who are virologically and immunologically responding to HAART.

Toelichting onderzoek

Achtergrond van het onderzoek

Patients from The Netherlands and Belgium included in this trial have started HAART either during primary or chronic infection, have an undetectable
plasma viral load and a CD4+ T-cell count ¡Ý 500 cells per mm3. Three phases are considered. During the immunization phase, the DC-based cellular vaccines are administered when patients are still on HAART. During this phase, the numbers of HIV-specific CD4+ and CD8+ T cells are expected to increase, while the viral replication is still controlled by HAART. HAART is discontinued two weeks after the last vaccine injection. During this analytical therapy interruption phase careful monitoring of
the plasma viral load and the CD4+ T-cell counts is carried out. The previously increased levels of HIV-specific
CD4+ and CD8+ T cells are expected to persist and control the HIV replication. Anti-retroviral therapy is resumed (re-HAART phase) either when CD4+ T-cell count decreases below 50% of the baseline value (i.e. at the time of study entry) or when re-treatment is considered as necessary, according to the guidelines for the use of anti-retroviral agents in HIV-1 infected adults and adolescents, developed by the Panel on Clinical Practices for Treatment of HIV Infection (http://www.AIDSinfo.nih.gov).

Doel van het onderzoek

This study is designed to determine safety and toxicity of the administration of autologous DC
electroporated with mRNA encoding the early expressed HIV-1 proteins Tat, Rev and Nef in patients who
are virologically and immunologically responding to stable HAART.

A total of seventeen evaluable patients will be recruited. In previous pilot clinical trials involving
vaccination with DC presenting various tumor antigens, no severe toxicity (Grade III or Grade IV) was
observed. Accordingly, we can postulate that for the present vaccine the maximum toxicity rate of grade
III (other than skin or flu-like symptoms) or grade IV will not exceed 5% to 10%. The total number of
patients expected to complete this study is 16. If no patient experienced such toxicity (0%, 80%
confidence interval 0%-11%), then one may conclude with more than 80% confidence that the real
toxicity rate is less than 11%. If one case of grade III (other than skin or flu-like symptoms) or grade IV
toxicity occurs, the toxicity rate will still be considered as acceptable. Two cases of such toxicities will
result in discontinuation of the study.

We will assess the ability of these mRNA electroporated DC to enhance the HIV-specific T-cell responses
against Tat, Rev and Nef on the one hand. On the other hand, we will analyse the kinetics of the HIV
viral load rebound after ATI and the duration of the period off HAART. Given the small number of
included patients, we do not expect to be able to draw any statistically significant conclusions. The
immunological and virological data will be analysed descriptively.

Onderzoeksopzet

1. December 2006 start study entry;

2. December 2008 inclusion completed;

3. March 2009 immunizations completed;

4. December 2010, follow-up completed, stop study.

Onderzoeksproduct en/of interventie

Four monthly immunizations with autologous dendritic cells, expressing TAT, REV and NEF, ten million each. Sub cutaneous and intra-dermal application of the formulations at three distinct sites.

Control group: No intervention;

Control to stop therapy from historical cases (Tristan project).

VACCINATION PLAN

Dendritic cells:

Each DC-based vaccine will be administered at a dose of 10 x 106 DC on every day of vaccination. These DC will either be electroporated with Tat, Rev or Nef encoding mRNA. For details concerning agent composition and formulation, see the Investigators Brochure.

Vaccine Administrations:

1. Patients will receive four sequential immunisations every four weeks;

2. On each vaccination day, the three autologous DC vaccines (10 x 106 DC electroporated with Tat, Rev
or Nef encoding mRNA) will be administered intradermally (50% of the vaccine volume) and subcutaneously (50% of the vaccine volume) through two separated needle tracts at the antero-median
side of an arm or a thigh. One limb will receive the whole of the vaccine at every treatment day.
Injection sites will be kept constant for each of the antigens;

3. All patients will be treated as outpatients and must be observed for 2 hours following injection. Drugs
and equipment will be immediately available to treat possible anaphylaxis. Beginning the day of each
vaccination and for the next 6 days, patients will be asked to take and record their axillary temperature,
all medications taken, as well as any symptom they may experience, on a diary card given to them the
day of each injection. They will return this diary card to the clinic for checking and completion the day
of the next visit.

Analytical therapy interruption:

Two weeks after administration of the last vaccine, all patients will be submitted to an analytical treatment
interruption (ATI). During the ATI, patients will be carefully monitored by clinical examination and blood
analyses including the assessment of HIV-specific T-cell responses, total CD4 T-cell count and plasma viral
load. HAART will be resumed either when the CD4+ T-cell count decreases below 50% of the baseline value

(i.e. at the time of study entry) or when re-treatment is considered as necessary, according to the guidelines for the use of anti-retroviral agents in HIV-1 infected adults and adolescents, developed by the Panel on Clinical Practices for Treatment of HIV Infection (http://www.AIDSinfo.nih.gov).

Clinical follow up:

1. During the immunization phase, patients will be subjected to a clinical evaluation the day of and one
week after vaccination;

2. Following ATI, all patients will undergo clinical re-evaluation, including physical examination and
laboratory blood tests, at regular time intervals (every week for the first month, every two weeks for the
next month, monthly for another 10 months and every 3 months during the subsequent year);

3. All patients must agree to inform the investigator about the evolution of their disease related health
status after completion of the study. Patients will be offered long-term follow-up at the study centers.

Dose Limiting Toxicities (DLT):

1. DLT is defined as grade III (other than skin or flu-like symptoms) or grade IV treatment-related
toxicity;

2. To be dose limiting, an adverse event must be definitely, probably, or possibly related to the
administration of the study agent;

3. If DLT is observed in a patient, he/she will be removed from the study.

Ancillary Therapy:

1. During the study, patients may not receive treatment with interferon-¦Á, interleukin-2, continuous
systemic corticosteroids, other immunosuppressive agents including chemotherapeutic agents or other
immunotherapeutics. Treatment with non-steroidal anti-inflammatory drugs or antihistamines is not
recommended but may be instituted at the discretion of the treating physician if clinically necessary.
Investigators may prescribe all other concomitant medications or treatments deemed

necessary to
provide adequate patient care;

2. All prescription and nonprescription concomitant medications must be recorded in the case report form,
listing generic name, indication, dose, route of administration and dates of administration.

Dose Adjustments:

No dose adjustments during the study are planned.

Contactpersonen

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

1. HIV-1 seropositive;

2. >1 year on stable HAART;

3. Viral load: <50 copies/ml for >3 months;

4. CD4 T cells: >500 cells/ul for >3 months and a nadir of > 300 cells/ul;

5. >18 years of age.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

1. Acute or serious illness <14 days before study entry;

2. HIV viral load >50 copies/ml in 3 months before entry;

3. CD4 T cell count <500 cells/ml;

4. History of lymph node irradiation;

5. Prior use of any HIV vaccine and/or non-established therapy;

6. History of allergy to neomycin or history of other serious allergic reaction;

7. Pregnancy and breastfeeding;

8. History of immune modulators or suppressors <30 days prior to study entry;

9. Active drug or alcohol abuse or dependence or psychiatric abnormality that would interfere with adherence to the study requirements;

10. Known HIV-1 seroconversion within one year prior to study entry, infection with HBV, HCV or HTLV-I or II.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Parallel
Toewijzing:	N.v.t. / één studie arm
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving gestopt
(Verwachte) startdatum:	01-12-2006
Aantal proefpersonen:	17
Type:	Werkelijke startdatum

Ethische beoordeling

Positief advies

Datum:	03-02-2010
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL2080
NTR-old	NTR2198
Ander register	VUB-05-001 : MEC-2005-227
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Resultaten

Samenvatting resultaten
Allard S.D., Pletinckx K., Breckpot K., Heirman C., Michiels A., van Baalen C.A., Gruters R.A., Osterhaus A.D.M.E., Lacor P., Aerts J.L., Thielemans K. (2008) Functional T-cell responses generated by dendritic cells expressing the early HIV-1 proteins Tat, Rev and Nef. Vaccine 26,

3537-3541.