Immunity after yellow fever vaccination in HIV positive travelers - YELLAR study

Published: 02-08-2012
Last updated: 26-04-2024

Primary Objective: To determine the height and duration of viremia, the seroconversion rate and the level of neutralising antibodies in relation to - the actual number of CD4 positive cells- the nadir of CD4 positive cells- the duration of CD4 count...

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

Summary

ID

NL-OMON39974

Source
ToetsingOnline

Brief title
YELLAR study

Condition

- Viral infectious disorders

Synonym
Yellow Fever Infection

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: HIV, Travelers, Yellow fever vaccination

Outcome measures

Primary outcome

The height and duration of viraemia, the seroconversion rate and the level of

neutralising antibodies in relation to:

- the actual number of CD4 positive cells

- the nadir of CD4 positive cells

- the duration of CD4 count above 200

- and the viral load of HIV

Secondary outcome

Local and systemic side effects of yellow fever vaccination in HIV positive

patients.

A comparison of all endpoints in the HIV positive group compared to the healthy

controls.

Study description

Background summary

The 17D-Yellow Fever vaccine is a live attenuated vaccine. The vaccine has been proven safe and effective; however, in the immunosuppressed, there is a theoretical risk of neuroinvasion and encephalitis. The exact pathogenicity of these SAEs has not been elucidated up to date. Possibly, those are the result of a hampered immunologic response in the host, resulting in an increased replication of the virus.

A recent retrospective study with a Swiss cohort of 102 HIV infected patients vaccinated with the yellow fever vaccine (YFV) reported that HIV positive vaccinees have lower rates of seroconversion, and lower geometric mean titers

(GMTs) of neutralizing antibodies (NAs) compared to healthy controls. A study from Mali reported no adverse events in their cohort of 115 HIV positive patients vaccinated with YFV.

In the Swiss study as well as in other studies of yellow fever vaccination in HIV positive vaccinees, neither adverse events (AEs) or severe adverse events (SAEs) have been described to occur at a more frequent rate compared to healthy vaccinees. These studies were however not powered to detect differences in serious SAEs, because these happen at very low rates; 0.4/100.000 vaccinees develop yellow fever vaccine associated viscerotropic disease (YEL-AVD) which resembles the clinical course of yellow fever infection, and 0.8/100.000 develop yellow fever vaccine associated neurotropic disease (YEL-AND).
In a population of elderly vaccinees, both local as well as systemic adverse events occurred at a lower rate compared to young vaccinees, whereas severe adverse events are known to occur more often in this population. Possibly, a hampered initial response results in lower rates of adverse events.

In response to yellow fever 17D infection, a cascade of immunologic responses follow. This is initiated by the formation of TNF alpha and type I interferons after binding to toll like receptors (TLRs) 2,7,8 and 9. Through stimulation of TLRs, both cellular (through Th1 cells) and humoral (through Th2 cells) responses are triggered. We would expect a hampered response of these Th1 and Ths cells among HIV infected patients, as the number of CD4+ cells declines. This relationship has been described in the Swiss cohort (3).
A recent study has however described antibody responses to be independent of CD4 count but strongly determined by the presence of plasma HIV-RNA. (18). By measuring viraemia and neutralising antibodies in relation to CD4 count and the presence of plasma HIV-RNA, we aim to add to insights into the predictive factors for an effective immune response. Additionally, we will measure several parameters indicative for an activated innate immune response as well as T cell responses. By comparing all these parameters in HIV positive patients and healthy controls at set timepoints after vaccination, we aim to acquire a comprehensive overview of the immune response to the YF 17D vaccine in HIV positive patients.
We aim to assess whether the immune response is delayed or lower in HIV positive patients compared to healthy controls. This gives an indication whether the yellow fever vaccine is a risk for SAEs in HIV positive patients.
In our center, approximately 10 HIV positive patients with CD4 counts ranging from 200-500 are vaccinated annually with the yellow fever vaccine.

Study objective

Primary Objective:
To determine the height and duration of viremia, the seroconversion rate and the level of neutralising antibodies in relation to
- the actual number of CD4 positive cells
- the nadir of CD4 positive cells

- the duration of CD4 count above 200
- and the viral load of HIV

Secondary Objective(s):
To evaluate the local and systemic side effects of yellow fever vaccination in HIV positive patients.
To evaluate the innate response and T cell responses following yellow fever vaccination in HIV positive patients.
To compare all responses between HIV positive patients and healthy controls.

Study design

Observational case-control study. The duration of the study will be approximately 2 years. The setting is either the Academic Medical Center, University hospital Leiden or the Havenziekenhuis in Rotterdam.

Study burden and risks

It is beneficial for subjects to be aware of their protection against yellow fever virus, if needed additional preventive measures can be taken in the case of travel to a yellow fever endemic area. In the future, better pre-travel advice can be formulated in travelers with HIV needing a yellow fever vaccination.

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

> 18 years
Indication for first yellow fever vaccination
Travel to a yellow fever endemic area within one year
Stable CD4 counts between 200 and 500 for at least two one year (2 measurements at half yearly clinical visits) and certain travel to yellow fever endemic area, even if travel has not been planned.

Exclusion criteria

< 18 years
Previous yellow fever vaccination

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	08-06-2013
Enrollment:	60
Type:	Actual

Ethics review

Approved WMO Date:	02-08-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-01-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-06-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-08-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-02-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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
CCMO	NL40624.018.12