TCR repertoire analysis after Hepatitis A vaccination

Published: 18-03-2024
Last updated: 10-01-2025

In this study we aim to answer the question whether TCR diversity becomes limiting at older age and thereby leads to impaired responses to novel antigens. While many studies have suggested a contraction in TCR diversity with age, a one-to-one…

Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON56630

Source
ToetsingOnline

Brief title
TRAIN

Condition

- Other condition
- Immune disorders NEC

Synonym
Immune response with age, TCR repertoire

Health condition

Ageing

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: NWO

Intervention

Keyword: Ageing, Hepatitis A, T cell receptor diversity, Vaccine

Outcome measures

Primary outcome

Determine TCR repertoire diversity of antigen-specific T cells to Hepatitis A

in young and older people after vaccination with VAQTA Adult

Secondary outcome

• Determine the gene expression profile of antigen-specific T cells to

Hepatitis A in young and older people after vaccination with VAQTA Adult

• Determine the frequency of antigen-specific T cells to Hepatitis A before and

after vaccination

• Phenotypic analysis of antigen-specific B and T cells to Hepatitis A before

and after vaccination

• Compare the B cell repertoire diversity and selection in old and young people

after vaccination with VAQTA Adult.

Study description

Background summary

Ageing is generally associated with dysfunction in both the adaptive and the innate immune system, which renders the elderly population more susceptible to infectious diseases. Additionally, reduced vaccine response is observed in the elderly, which limits preventative care. The ability to induce protection with the influenza vaccine, for example, declines with age, with an efficacy between

70% and 90% in children and adults, dropping to 30-50% for those over 65 years of age. Together, the declining immune function and reduced vaccine efficacy leave the elderly susceptible to infectious diseases. One amongst the many effects of ageing on the immune system is the compromised ability of T cells to respond to novel infections and manage chronic infections. It is generally regarded that these decreased immune responses in the elderly are due to reduced T-cell diversity at older age owing to many factors, such as thymic involution and peripheral clonal expansion of antigen-specific T cells.

The ability to mount a T cell response to new antigens is dependent on T cell frequency and functionality and T cell receptor (TCR) diversity. TCRs are highly polymorphic heterodimers which are responsible for the recognition of antigens. The diversity of the TCRs recruited in response to an infection is directly related to the outcome of the infection wherein low diversity TCR repertoires allow for more rapid viral escape.

Many studies have demonstrated a loss of TCR repertoire diversity with age. Olga et al showed that with age there is a loss of diversity in the T cell pool and that the more expanded clones make up an increasing fraction of the T-cell pool [6]. This is somehow expected, as with age i) the thymus, which is responsible for the generation of T cells with new specificities, undergoes involution, and ii) the number of infections an individual has undergone increases. Hence, the number of clonal expansions in the T-cell repertoire increases, resulting in an overall loss of TCR diversity. More specifically in the naïve T-cell pool, a study has shown that with age, high frequency clones (T cells with the same TCRβ chain) in the naive CD4 T cell pool make up a larger fraction of the total TCRβ diversity, suggestive for a reduced diversity in the naïve TCR repertoire.

These changes in the T-cell pool are generally held responsible for the impaired immune responses that are typically observed in older individuals. The idea is that due to *holes* in the naïve T cell repertoire, older individuals have an impaired capacity to respond to new antigens. Indeed, a study conducted in old mice demonstrated restricted TCR repertoire diversity of the epitope-specific T cell pool in an influenza model. The epitope-specific T cells that were present in low frequencies in the naive T-cell compartment of younger mice were found to be less frequent at older age [8]. It remains unknown whether a similar effect occurs in humans. It is imperative to realize that conclusions from mouse models cannot be directly applied to humans as the size of the T cell compartment and the mechanisms of maintenance of T cells differ between mice and men. This motivates a separate investigation in humans.

Study objective

In this study we aim to answer the question whether TCR diversity becomes limiting at older age and thereby leads to impaired responses to novel antigens. While many studies have suggested a contraction in TCR diversity with

age, a one-to-one comparison between the TCR diversity between young and old age groups, in response to a new antigenic stimulus (here, vaccine) has not been made. This study design will help us to study the difference in the TCRs recruited from the naïve T cell pool in response to an antigenic stimulus and will thus provide insight into the functional loss of TCR diversity with age.

Study design

This study is divided into two parts- Phase I and Phase II.

The first part of the study is called Phase I is an observational study with invasive procedure in the form of blood draws.

In Phase I, we will recruit participants previously vaccinated with Hepatitis A to determine the frequency of Hepatitis A specific T cells, and the blood volume required to sort these cells in sufficient numbers for TCR repertoire analysis. We also want to quantify the frequency of cells that are cross-reactive/falsely reactive to Hepatitis A. Therefore, we will also recruit healthy adults naïve to Hepatitis A (i.e. no previous vaccination or infection record of Hepatitis A). Recruiting participants who have been previously vaccinated allows us to reduce number of participants receiving a vaccine as an intervention in our study.

In Phase II, we will address the main objective of this study.

To this end, we will recruit a cohort of Young (18-30 years) and Older (65-80 years) healthy individuals naïve to Hepatitis A. CMV and Hepatitis A naïve individuals will be vaccinated with two doses of VAQTA Adult® vaccine and their Hepatitis A specific TCR repertoire will be analysed.

Invasive procedures: In Phase I, maximally two blood samples and in Phase II, maximally five blood samples will be taken from all participants. In addition, with each visit, participants are asked to fill in a short questionnaire about their health.

Interventions in this study: 20 (10 young and 10 older) participants from Phase II will be vaccinated with two doses of the VAQTA Adult® vaccine which is a vaccine against Hepatitis A virus.
Phase II can be described as an observational, cross sectional study with an intervention and invasive procedures.

For this research it is essential that we follow the antigen-specific T-cell response to a pathogen that participants have not encountered before and do not encounter during the study. Hepatitis A is a low incidence disease in the Netherlands with an average of 142 cases per year between 2013 and 2020 11. Vaccination against Hepatitis A is not mandatory in the Netherlands but is

recommended as a travel vaccine for certain countries. Thus, we regard it feasible to recruit enough participants who are immunologically naive to Hepatitis A, who can receive the vaccination for the first time. This logic dictates the choice of vaccination in this study.

Here, we use VAQTA as a tool to induce an immune response to a new antigen in Phase II participants. We are not addressing the *diagnostic, prophylactic or therapeutic potential of the medicinal product nor its pharmacokinetic or pharmacodynamic profile* as defined by Regulation (EU) No 536/2014. VAQTA Adult® already has marketing authorization in the EU, for both age groups, and we use it as a non-investigational product that is used as a means to follow antigen-specific T cells, in order to study the effect of ageing on the immune response.

Study burden and risks

20 Participants of Phase II will receive 2 doses of the VAQTA Adult® vaccine against Hepatitis A virus. The VAQTA Adult® vaccine is regarded safe for both age groups and could possibly benefit the health of vaccinees by providing protection against Hepatitis A. Participants in Phase I will donate blood a maximum of two times, while participants in Phase II will donate blood five times maximally. The risks of this study are minimal as VAQTA is an EMA/FDA approved vaccine and the main burden on the participants is to receive the two doses of vaccine, the blood draws and the time consumed for the visits to the hospital.

Contacts

Public
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584CX
NL
Scientific
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584CX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

For the Hepatitis A positive cohort (only in Phase I)
To be eligible for inclusion in the Hepatitis A seropositive cohort of this study, a subject must meet all of the following criteria:
Participants
• have recently (< 12 months) been vaccinated with Hepatitis A vaccine
• are able to follow the protocol of the study during the study period

For the Hepatitis A sero-negative cohort (of both Phase I and II)
To be eligible for inclusion in the Hepatitis A seronegative cohort, a subject must meet all of the following criteria:
Participants are
• without previous record of vaccination/ infection with Hepatitis A
• able to follow the protocol of the study during the study period

Exclusion criteria

Broadly , we want to exclude participants with a CMV infection and participants with diseases or lifestyle that have a negative impact on the immmune system. To insure this we exclude the participants with

1. Infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV);
2. Other current serious infections, such as malaria or a sexually transmitted disease (STD);
3. Infection with CMV
3. Active allergy;

4. Asthma, Diabetes, COPD;
5. Any previous known hepatic illness
6. Autoimmune diseases, such as rheumatoid arthriti
7. A body weight less than 50 kg;
8. Excessive alcohol consumption (more than 36 drinks per week for men, for women more than 24 drinks per week);
9. Medication use, apart from if the medication is known to affect the immune system; and painkillers, if used lessmore than twice per week (paracetamol, ibuprofen, aspirin);
10. Drug use;
11. Heart problems for which the subject is currently undergoing treatment;
12. Kidney complaints for which medication is currently used;
13. Shortness of breath or chest pain, at rest or with exertion;
14. Cancer or a history of cancer;
15. Pregnant and Nursing women
16. Blood donors who are not willing to stop donating blood in the duration of this study.
17. People with allergic reaction/sensitivity towards neomycin, latex or formaldehyde.
18. People with Anemia.

The reasoning for this is further elaborated in section 4.3 of C1 Onderzoeksprotocol.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-04-2024
Enrollment:	145
Type:	Anticipated

Ethics review

Approved WMO Date:	18-03-2024
Application type:	First submission
Review commission:	METC NedMec

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	NL82935.041.23