Generation of broadly neutralizing antibodies for the development of an enterovirus immunotherapy

Published: 20-01-2017
Last updated: 11-04-2024

Primary Objective: To isolate B-cells producing bNAbs against EVs from healthy human individuals and to generate bNAbs from these B-cells for the development of a novel EV immunotherapy. Secondary Objective(s): To further elucidate the humoral...

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

Summary

ID

NL-OMON45608

Source
ToetsingOnline

Brief title
THEIS Study

Condition

- Viral infectious disorders

Synonym
enterovirus infections, viral infections

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: ZonMw

Intervention

Keyword: broadly neutralizing antibodies, enterovirus, immunotherapy

Outcome measures

Primary outcome

From each donor blood will be withdrawn in order to collect serum and PBMCs.

The sera will be used to determine nAb titers against a panel of clinically

relevant EVs, using a cytopathic effect (CPE) reduction assay. On the basis of

the neutralizing activity in the sera, paired PBMC samples will be selected for

isolation of bNAb producing B cells by single cell sorting.

Secondary outcome

None

Study description

Background summary

HUMAN ENTEROVIRUSES POSE A SERIOUS THREAT TO GLOBAL PUBLIC HEALTH
Viruses belonging to the genus Enterovirus of the family of Picornaviridae are major causes of serious disease in neonates and very young children worldwide. The most well-known member of this family, poliovirus, is close to extinction as a result of the World Health Organization (WHO) eradication campaigns. However, the related enterovirus (EV) 71 has started causing massive outbreaks in Asia with ten thousands of cases of severe neurologic disease and thousands of cases of infant death. Another clinically relevant EV is EV68, which recently caused a nationwide outbreak of severe respiratory disease in the USA. In addition, coxsackie- and ECHO viruses are leading causes of sepsis-like illness and aseptic meningitis. These EVs cause 10-15 million of symptomatic infections in the USA each year, with around 75.000 cases of aseptic meningitis. Enterovirus-associated disease and fatalities have brought a heavy economic burden to regions with high prevalence. Furthermore, the emergence of novel (sub)genotypes giving rise to serious outbreaks poses a global public health threat that should not be neglected.

NO VACCINES OR ANTI-VIRAL DRUGS AGAINST ENTEROVIRUSES ARE AVAILABLE

The global polio eradication program has unintentionally overshadowed the clinical relevance of other non-polio EVs. As a consequence, the development of vaccines and therapies against these viruses has been lagging behind and even in developed countries children die of non-polio EV infections. Intravenous immunoglobulin (IVIg) administration is sometimes used to treat severe EV infections, based on the protective effect of anti-EV neutralizing antibodies (NAbs) expected to be present in the IVIg formulation. However, it is generally not known whether titers of NAbs against the causative EV type are high enough in the IVIg pools (derived from >1000 plasma donors). The massive outbreaks of EV71 in Asia have triggered the development of EV71 vaccines and monoclonal antibodies (MAbs). However, these approaches do not take into account the broad range of clinically relevant EVs causing disease elsewhere. Also, vaccines cannot be applied directly in newborns, the most vulnerable group for severe EV infections, because of their incompletely developed immune system.

Cross-reactive epitopes as targets for therapy development
Neutralizing antibody responses are unavoidably elicited against the immunologically dominant sites of EVs and such responses determine the serotype. A significant proportion of the immunologically dominant determinants in EVs are present in one of the structural proteins known as VP1. The epitopes presented in the surface exposed loops of VP1 are highly diverse and susceptible to antigenic drift which leads to the generation of escape mutants. However, heterologous NAb responses have been observed in animal and human sera and nAbs with a cross-neutralizing reactivity among polioviruses have been isolated. This provides evidence of the presence of conserved epitopes among EVs, which represent highly interesting targets for the development of broadly reactive immunotherapies. Pepscan analyses have revealed the location of several of those (linear) conserved epitopes.

The role of bNAbs in protection or clearance of heterologous infections has been recognized in recent years and advances have been made in the development of immunization strategies for the induction of bNAbs against human immunodeficiency virus (HIV) and Influenza. These advances have triggered the exploration of potent and safe immunotherapy regimens that could provide a long-term remission for HIV. These same promising avenues prompted us to isolate and characterize bNAbs against EVs from human individuals and to use these as a scaffold for production of bNAbs for an EV immunotherapy.

Only a few studies in the EV research field on induction of bNAbs have been described, of which the majority focuses on bNAbs among polioviruses of type 1, 2 and 3. Knowledge on bNAbs against enteroviruses and their target epitopes is therefore very limited. Our approach of isolating EV bNAb producing B-cells from human individuals is new and has not been published before. Characterization of bNAbs and their antigenic sites will therefore contribute to a better understanding of the humoral response against EVs and will be an important step towards development of an EV immunotherapy.
Enteroviruses are highly prevalent, which is reflected by the high percentage

of seropositive children (above 5 years) and adults. In the Netherlands, for instance, 80% of adults has high nAb titers against EV71. The IgG variable regions of bNAbs against influenza and HIV, isolated from adult donors, were shown to be highly mutated, indicating that these bNAbs underwent multiple rounds of affinity maturation. Therefore, adults with a high probability of repeated exposure to EVs (via frequent contact with children) are expected to be a suitable source of bNAbs against EVs.

Study objective

Primary Objective:
To isolate B-cells producing bNAbs against EVs from healthy human individuals and to generate bNAbs from these B-cells for the development of a novel EV immunotherapy.

Secondary Objective(s):
To further elucidate the humoral immune response to EVs by defining the potency of epitopes we selected to capture B-cells to induce bNAbs against EV in humans

Study design

The design of this study will be a prospective observational study. Eligible healthy adult volunteers (aged 18-65 years) will be informed on the study and asked for informed consent. Healthy volunteers will be recruited at the Academic Medical Center (AMC), Amsterdam via distribution of a poster, presentation of the research proposal during work meetings and personal communication. After written consent, study participants will be invited for a one-time venous blood sampling (a maximum of 21 ml blood). Blood samples will be labelled with blinded code numbers to prevent identification of the blood donors. Blood samples will be further handled and stored at the AMC Department of Medical Microbiology (headed by Prof. Dr. M.D. de Jong). Samples will be stored under the above mentioned (anonymous) code for 5 years.

Study burden and risks

In total 21ml of blood will be sampled from each adult donor via a single venupuncture by well-trained medical staff. We therefore do not expect a more than negligible risk. Participation will consume a limited amount of time and subjects might experience some level of discomfort during the blood withdrawal. Isolation of bNAbs from these donors will be the first big step in the development of an EV immunotherapy for the treatment of life threatening EV infections in neonates and young children. Our approach would therefore greatly improve patient care and thus reduce disease burden and child suffering worldwide.

Contacts

Public
Academisch Medisch Centrum

Meibergdreef 5
Amsterdam 1105 AZ
NL
Scientific
Academisch Medisch Centrum

Meibergdreef 5
Amsterdam 1105 AZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Age of 18-65 yrs.
Healthy condition (no immunodeficiency).
Written informed consent.

Exclusion criteria

see above

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	25
Type:	Anticipated

Ethics review

Approved WMO

Date:	20-01-2017
Application type:	First submission
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	NL60160.018.16