The role of PF4-specific B cells in patients with Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT)

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To enhance our knowledge of the molecular nature, induction and regulation of the autoantibody and B cell response involved in/responsible for the induction of VITT

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

Summary

ID

NL-OMON57278

Source
ToetsingOnline

Brief title
VITT

Condition

- Autoimmune disorders

Synonym
the development of blood clots in the veins after vaccination, Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT)

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: ImmuneHealthSeed programma door Health Holland

Intervention

Keyword: Autoimmunity, B cells, COVID-19, vaccine

Outcome measures

Primary outcome

Isolation of PF-4-specific B cells from peripheral blood, determination of PF-4 reactive B cell receptor sequences/repertoires, generation of monoclonal, PF-4 specific antibodies, and phenotypic characterization of the PF4-specific B cell response.

Secondary outcome

n.a.

Study description

Background summary

To date, the induction of autoimmunity and in particular autoreactive B cell responses is incompletely understood. During the corona pandemic, protection against the SARS-Cov-2 virus was generated by the administration of vaccines. 4 different vaccines were administered to the majority of the Dutch population. Two of these, both based on an adenoviral vector, appeared to induce a severe side effect called Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT). VITT occurred in a very small number of individuals and was found to be strongly associated with high-titer IgG autoantibodies directed against a cationic platelet chemokine, platelet factor 4 (PF4). It has been hypothesised that components from the vaccine could interact with PF4, thereby leading to the activation of PF4-specific B cells. A similar mechanism has been described for heparin-induced thrombocytopenia (HIT) and for spontaneous heparin-induced thrombocytopenia (HIT) syndrome, a form of *autoimmune* HIT (aHIT). Both HIT and aHIT share clinical features with VITT. Little is known, however, on how VITT is induced precisely and how it is different, on the B-cell and antibody level, from HIT or aHIT. Of note, also 2-6% of healthy individuals harbour IgG anti-PF4 antibodies. Here, we intend to study the antibody response and the B cell-receptor profile of PF4-specific B cells in patients that have been diagnosed with VITT or HIT/aHIT to better understand the molecular details and reactivity patterns of PF4-directed antibodies. Using VITT and the PF4-specific

B cell response as a model, we expect that important insights can be generated on how autoreactive B cell responses are induced, which has direct relevance for systemic autoimmune diseases in other fields, amongst which rheumatology.

Study objective

To enhance our knowledge of the molecular nature, induction and regulation of the autoantibody and B cell response involved in/responsible for the induction of VITT

Study design

Observational study, single centercentre

Study burden and risks

The primary procedure for study participants is a single blood draw and completion of a questionnaire. VITT and aHIT/HIT patients will be identified through database records available at Sanquin, Amsterdam. These (former) patients will be contacted by letter. To respond, patients will be provided with a return envelope or can actively make contact via email or phone. Eligible (former) patients are expected to live in different parts of the Netherlands. For patients who live at >25 km distance from the LUMC, a trained member of the research team will visit study participants at home to draw blood once (100mL total). Patients who live within a distance of <25km from the LUMC will be asked to come to the LUMC. Age- and sex-matched healthy donors will be recruited by advertising within the LUMC (e.g. local blackboards at the restaurant and the shopping area *Leidse Plein*, information screens at the outpatient clinic of the rheumatology departments). In all cases, the risk for study participation relates to a single blood draw by routine venous puncture. Possible side-effects are local hematoma and discomfort due to the puncture. These risks are considered negligible.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Age 18 years or older
- Ability to understand the patient information form and ability to provide written informed consent.

The criteria used for allocation of patients to their specific study group are as follows:

Criteria specific to VITT patients:
- Diagnosed with VITT based on diagnostic laboratory testing (performed by Sanquin) after vaccination with ChAdOx1 nCoV-19 or Ad26.COV2.S

Criteria specific to aHIT/HIT patients:
- Diagnosed with HIT following exposure to heparin or with spontaneous HIT/aHIT. Diagnosis based on diagnostic laboratory testing (performed by Sanquin).

Exclusion criteria

- Individuals who fail to meet the inclusion criteria.
- Individuals who have donated 50 ml of blood (or more) less than two weeks prior to the respective time-point for any reason (such as routine clinical care, participation in another study, blood donations for the blood bank, etc.)
- Individuals with a self-reported or otherwise known diagnosis of severe

anemia (blood hemoglobine < 6 mmol/L).

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-01-2025
Enrollment:	60
Type:	Anticipated

Ethics review

Approved WMO

Date:	28-01-2025
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	NL86771.058.24