B cell monitoring in young and elderly healthy donors, young smokers, elderly smokers and patients with stable coronary artery disease

Published: 04-02-2019
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Main objectiveComparison of:- circulating B cell subsets,- immunoglobulin subsets,- B cell functionality (by means of ex vivo challenges),- and other relevant immune cellsbetween young healthy donors (aged 18-25 years), elderly healthy donors (>...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Coronary artery disorders
Study type	Observational invasive

Summary

ID

NL-OMON47964

Source
ToetsingOnline

Brief title
B cell monitoring in healthy donors, smokers and CAD patients

Condition

- Coronary artery disorders

Synonym
cardiac arrest

Research involving
Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research

Source(s) of monetary or material Support: Investigator Sponsored Study;with support from Vaccination in Atherosclerosis grant

Intervention

Keyword: B cell, coronary artery disease, regulatory B cell

Outcome measures

Primary outcome

Circulating B cell subsets:

- B1 cells

- Naive B cells

- Transitional B cells

- Non-class-switched memory B cells

- Class-switched memory B cells

- Plasmablasts and plasma cells

- Regulatory B-cells

- Age associated B-cells

Immunoglobulin classes:

- total IgG, IgM, IgE. oxLDL IgG1, IgG2 + IgM.

- oxLDL specific IgM and IgG ELISpot

B cell functionality, by means of ex vivo challenges, evaluating:

- Pathways:

* TLR7 stimulation

* TLR9 stimulation

- Readouts:

* Cellular mRNA (isolated B-cells)

* Circulating cytokines (e.g. IL-10 and IL-35 + IL-12p70, IL-1*, TNF*, IL-6,

IL-17)

* Secreted cytokines after stimulation (e.g. IL-10, IL-35, TGF*,

pro-inflammatory cytokines)

* Intracellular cytokines (e.g. IL-10, IL-35)

* Surface markers on B-cells (non-lineage markers) (e.g. PD-1, PDL-1, PDL-2,

TIM-1)

- Other relevant immune cells including, but not limited to:

o CD4+ T cells (Th1/Th2/Th17/Treg), CD8+ T cells, inflammatory monocytes,

neutrophils, basophils

- Routine laboratory blood tests:

o Chemistry

o Hematology

- Immune cells in adipose tissue

Secondary outcome

N.A.

Study description

Background summary

Atherosclerosis is a chronic inflammatory disease of the artery wall. Treatment of atherosclerosis has been based on lipid-lowering therapies for years, reducing multiple risk factors. Adaptive immunity plays a key role in the pathogenesis of atherosclerosis. Accumulating evidence supports the idea that

immunization with antigenic proteins or peptides may reduce atherosclerosis. Modulation of the adaptive immune system may treat or prevent atherosclerosis, and lead to the development of more selective and less harmful interventions, while keeping host defense mechanisms against infections and tumors intact. Aging is one of the major drivers of atherosclerosis and with a rapidly increasing aging population, there is a huge need to enhance our understanding of immune responses during cardiovascular disease to develop the most effective therapeutic intervention for the patient.
Although the role of T cells in the development and progression of atherosclerosis has been extensively studied for decades, only recently the role of B cells has gained more attention. B cell subsets are found in human and murine atherosclerotic plaques. B cells have long been thought to have a general protective effect in atherosclerosis. However, recent studies have identified differential effects of different B-cell subsets. B1 cells are atheroprotective, mainly via the production of natural IgM antibodies that bind oxidized low-density lipoprotein and apoptotic cells. B2 cells are suggested to be proatherogenic, via production of IgG, secretion of TNF*, and activation of CD4 T cells. Finally, there is a minor subset of splenic regulatory B cells (Bregs) that protect against atherosclerotic inflammation by promoting the generation of Tregs and production of anti-inflammatory cytokines IL-10 and TGF-* and proapoptotic molecules. It is unknown whether Bregs are a permanently existing cell subset, or derived from B cells upon specific stimulation.

Study objective

Main objective
Comparison of:
- circulating B cell subsets,
- immunoglobulin subsets,
- B cell functionality (by means of ex vivo challenges),
- and other relevant immune cells
between young healthy donors (aged 18-25 years), elderly healthy donors (>60 years), young smokers (aged 18-25 years), heavy smokers (>45 years) and patients with stable coronary artery disease (>60 years).

Secondary objectives
- Development of optimal flow cytometry panels for identification of various B cell subsets;
- Setup of ex vivo B cell challenges for evaluation of B cell functionality.
- Immune cells in adipose tissue.

Study design

Single-center observational study

Study burden and risks

Subjects will be subjected to a single blood draw and fat biopsy, no benefits or risks are to be expected.

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

Healthy volunteers:
1. healthy male subjects (18-25 years or >60 years);
2. ability to participate, and willingness to give written informed consent and to comply with the study restrictions.
3. BMI 18 - 28
4. non-smoking, elderly non-smoking for at least 15 years.
smokers:
1. male subjects (18-25 years or >45 years)

2. ability to participate, and willingness to give written informed consent and to comply with the study restrictions.
3. BMI 18 - 28
4. volunteers >45 years: smoking for at least 15 packyears, volunteers 18- 25 years: at least * pack a day for 6 months. , CAD patients:
1. male patients (>60 years) with proven stable atherosclerotic coronary artery disease defined as having undergone a revascularization procedure followed by a period of at least one year without signs or symptoms of coronary artery disease;
2. having one of the following risk factors: high cholesterol, smoking, diabetes, hypertension, or familiar risk.
3. ability to participate, and willingness to give written informed consent and to comply with the study restrictions.
4. BMI 18 - 28

Exclusion criteria

healthy volunteers:
1. evidence of any active or chronic disease or condition (based on medical history, a physical examination, and vital signs) that could, in the opinion of the investigator, interfere with the study objectives;
2. evidence of any active or chronic disease or condition that affects the immune system.
3. having one of the following risk factors for CAD: high cholesterol, smoking, diabetes, hypertension, or familiar risk.
4. the use of any medication or vitamin/mineral/herbal/dietary supplement within less than 5 half-lives prior to study participation is prohibited, if the Investigator judges that it may interfere with the study objectives. The use of paracetamol (up to 4 g/day) is allowed;
5. body weight < 50 kg; BMI <18 or >28.
6. subject is pregnant or breast feeding;
7. smoking or current substance abuse, including alcohol and drugs;
8. loss or donation of blood over 500 mL within three months prior to participation;
9. unwillingness or inability to comply with the study protocol for any other reason., Smokers:
1. evidence of any active or chronic disease or condition (based on medical history, a physical examination, and vital signs) that could, in the opinion of the investigator, interfere with the study objectives;
2. body weight < 50 kg; or BMI <18 or >35;
3. substance abuse, including alcohol and drugs;
4. loss or donation of blood over 500 mL within three months prior to participation;
5. unwillingness or inability to comply with the study protocol for any other reason., CAD patients:

1. evidence of any active or chronic disease or condition other than stable CAD (based on medical history, a physical examination, and vital signs) that could, in the opinion of the investigator, interfere with the study objectives;
2. evidence of any active or chronic disease or condition other than stable CAD that affects the immune system.
3. body weight < 50 kg; BMI <18 or >28.
4. substance abuse, including alcohol and drugs;
5. loss or donation of blood over 500 mL within three months (males) prior to participation;
6. unwillingness or inability to comply with the study protocol for any other reason.
7. use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-03-2019
Enrollment:	150
Type:	Actual

Ethics review

Approved WMO

Date:	04-02-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	21-08-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	NL68390.056.19