The function of CX3CR1 receptors on circulating patrolling monocytes and other leukocytes determine the severity of emphysema in patients with ZZ genotype alpha-1-antitrypsin deficiency

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Primary Objective: To identify the variability in the circulation of the number of patrolling monocytes and their expression of CX3CR1 obtained from adult ZZ-AATD patients compared to spouse controls.Secondary Objective(s): (1) To identify if low…

Ethical review	Approved WMO
Status	Pending
Health condition type	Chromosomal abnormalities, gene alterations and gene variants
Study type	Observational invasive

Summary

ID

NL-OMON49069

Source
ToetsingOnline

Brief title
CX3CR1 functionality in patients with alpha-1-antitrypsin deficiency

Condition

- Chromosomal abnormalities, gene alterations and gene variants
- Lower respiratory tract disorders (excl obstruction and infection)

Synonym
hereditary deficiency of the protein alpha-1-antitrypsin, stretched lungs

Research involving
Human

Sponsors and support

Primary sponsor: Longziekten
Source(s) of monetary or material Support: Stichting AIR

Intervention

Keyword: alpha-1-antitrypsin deficiency

Outcome measures

Primary outcome

To identify the variability in the circulation of the number of patrolling monocytes and their expression of CX3CR1 obtained from adult ZZ-AATD patients compared to spouse controls.

Secondary outcome

1) To identify if low expression of CX3CR1 on PBMC in blood is associated with the severity of emphysema in subjects with ZZ-AATD. (2) To identify if expression of chemokine receptors other than CX3CR1 on PBMC in blood is associated with the severity of emphysema associated with the severity of emphysema in subjects with ZZ-AATD. (3) to identify if damage of pulmonary microvascular endothelial cells (pMVECs) reflected by the level of plasma E-selectin EMP (Endothelial Micro Particles, which are von-Willebrand negative) is correlated with any of the results identified in secondary objective nr 2.

Study description

Background summary

Alpha-1-antitrypsin (AAT) is the major serum anti-protease protein in humans.

Its genetic deficiency (AATD) lead in 1985 to the protease-antiprotease imbalance hypothesis to explain emphysema development. This hypothesis predicted that restoring the balance by intravenous AAT, isolated from healthy donors, would stop the progression of emphysema. To date, this has not been proven by an effect on lung function values (FEV1 or DLCO) in clinical trials. Therefore, we aim to investigate a new hypothesis. Based on our preliminary results we hypothesized that altered PBMC subpopulations and a consequent defect in the CX3CL1/CX3CR1 axis has a critical role in the pathogenesis of emphysema associated with inherited AAT deficiency. Furthermore, altered subsets of PBMC, like patrolling monocytes, may contribute to pulmonary microvascular endothelial cell (pMVEC) damage, which is enhanced in emphysema.

Study objective

Primary Objective: To identify the variability in the circulation of the number of patrolling monocytes and their expression of CX3CR1 obtained from adult ZZ-AATD patients compared to spouse controls.
Secondary Objective(s): (1) To identify if low expression of CX3CR1 on PBMC in blood is associated with the severity of emphysema in subjects with ZZ-AATD. (2) To identify if expression of chemokine receptors other than CX3CR1 on PBMC in blood is associated with the severity of emphysema associated with the severity of emphysema in subjects with ZZ-AATD. (3) to identify if damage of pulmonary microvascular endothelial cells (pMVECs) reflected by the level of plasma E-selectin EMP (Endothelial Micro Particles, which are von-Willebrand negative) is correlated with any of the results identified in secondary objective nr 2.

Study design

This is a case-control explorative study with an adaptive design for patients known with the diagnosis of ZZ-AATD. Controls are spouses of ZZ-AATD patients. To avoid analysis problems with mRNA sequence data, there should be about the same distribution of gender of numbers of spouse controls and ZZ-AATD cases.To compensate for effects of epigenetic factors on our hypothesis, we designed the study with spouses as controls. In our experience, spouses frequently join patients to our clinic, which is the only NFU-certified national reference center for the AATD condition.

Study burden and risks

An expected adverse event caused by pulmonary function testing may be tachycardia due to the required inhaled salbutamol. The tachycardia is transient and can be treated with medication if the subject asks for it.

A possible but rare adverse event caused by venous blood sampling may be

phlebitis of the sampled vene.

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

In order to be eligible for PBMC sampling in this study, a subject must meet all of the following criteria:
* Known ZZ-AATD genotype of study patient.
* Age between 30 and 75.
* Spouses with normal AAT genotype, as determined by a PCR kit: AlphaKit-Quickscreen (see section 6.3, study procedures in study protocol).
* Spouses must have normal gas transfer values of the lungs.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
* ZZ-AATD patient or spouse are current smoker.
* Patients or spouses who had any type of infection in the previous 3 months.
* Patients or spouses who are treated for any type of cancer.
* Any co-morbidity that in the opinion of the investigator may interfere with the interpretation of the primary outcome parameter of the study.

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):	07-09-2020
Enrollment:	56
Type:	Anticipated

Ethics review

Approved WMO

Date:	23-07-2020
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	NL74125.058.20