Scope change in vasculitis: the role of monocytes and macrophages in ANCA-associated glomerulonephritis

Published: 11-09-2020
Last updated: 15-05-2024

The main goal is to define whether macrophages from patients with AGN induce T-cell activation and migration due to their pro-inflammatory phenotype.

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

Summary

ID

NL-OMON55167

Source
ToetsingOnline

Brief title
MOMA study

Condition

- Autoimmune disorders
- Renal disorders (excl nephropathies)
- Vascular disorders NEC

Synonym
ANCA vasculitis with renal involvement, ANCA-associated glomerulonephritis

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis, Macrophages, Monocytes

Outcome measures

Primary outcome

The main study parameters are mRNA and protein expression levels of monocyte-derived macrophages in vitro and macrophages in situ in renal biopsies, and activation and migration of T-cells which are co-cultured with activated macrophages.

Secondary outcome

Secundary study parameters are T-cell receptor repertoires of migrated T-cells, HLA-DPB1*04:01 status in AGN patients, quality of life (SF-36, patient reported outcome measure, disease specific: AAV-PRO), fatigue levels (SF-36, AAV-PRO)

Study description

Background summary

Anti-neutrophil cytoplasmic antibodies (ANCA)-associated glomerulonephritis (AGN) is a rare autoimmune disease which results in end-stage renal disease in 25% of patients despite improved treatment options over the last twenty years. Even in periods with low disease activity, patients report a significantly reduced quality of life and high levels of fatigue. The pathophysiology of AGN remains enigmatic. The priming of neutrophils due to an unknown trigger is considered crucial, which leads to T-cell recruitment and activation, endothelial damage and vasculitis. Remarkably, in AGN, monocytes and macrophages are always present in vasculitis and/or granulomatous lesions. It is unknown whether macrophages attempt to repair or cause damage in AGN. Preliminary data showed that CXCL10, an important chemokine attracting T-cells, is increased in monocyte-derived macrophages from AGN patients. These findings and the abundant presence of macrophages in tissue lesions, indicate a central

pro-inflammatory role for macrophages in AGN. This study aims to investigate whether macrophages play a central role in AGN, continuously activating the immune system, as opposed to the long-held belief that neutrophils do so. Our hypothesis is that macrophages drive ANCA glomerulonephritis by activating T-cells and enhancing their migration towards vasculitic inflammation. Permanent macrophage activation could contribute to chronic elevation of fatigue levels.

Study objective

The main goal is to define whether macrophages from patients with AGN induce T-cell activation and migration due to their pro-inflammatory phenotype.

Study design

This study is designed as a multi-center observational study with longitudinal follow-up. Patients will be asked to have their blood drawn, to sample urine and fill out quality of life questionnaires. Next, in vitro monocyte-derived macrophage phenotype will be assessed by bulk RNA sequencing and macrophage induced T-cell activation and migration will be measured by a 3D system and a leucocyte extravasation essay. Macrophage phenotype in situ will be assessed by immunohistochemistry and immunofluorescence in renal biopsies (available for initial diagnosis) and by single-cell RNA sequencing of a small number (n=8) of fresh kidney biopsies derived from AGN patients and systemic lupus erythematosus (SLE) patients with renal involvement (n=3) who undergo a renal biopsy for diagnostic purposes. Surplus *healthy* kidney tissue derived from patients who undergo a (partial) nephrectomy for a renal cell carcinoma (n=3) will be used as control tissue for single-cell sequencing experiments.

Study burden and risks

There is no individual benefit from participation in this study. This study will increase knowledge about the etiology of ANCA vasculitis and may ultimately provide a target for new treatment options in the future. Minimal burden and risks are associated with participation. Patients who undergo an extra biopsy during a diagnostic renal biopsy, do not experience increased risk of adverse events as the maximum number of passes will be set at 3 biopsies.

Contacts

Public
Academisch Medisch Centrum

Meibergdreef 9

Amsterdam 1105AZ
NL
Scientific
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105AZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet following general and group-specific criteria:

General
1. Age: 18 years and older

Group-specific
Patients with ANCA-associated glomerulonephritis (AGN)
1. Diagnosed with granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA)
2. Renal involvement attributable to vasculitis
3. History of PR3/MPO positivity as determined by ELISA in the context of routine clinical care.

Hemodialysis controls
1. End stage kidney failure (ESRD) requiring hemodialysis

Active infection controls
1. Clinical diagnosis: pneumonia (CURB-65 score 2-5, imaging: X-thorax or CT-thorax showing infiltrates) or complicated urine tract infection

2. Admitted to the hospital <48h

Nephrectomy controls
1. Patients who undergo a (partial) nephrectomy for treatment of a renal cell carcinoma, who give consent for the use of surplus kidney tissue for research purposes

Patients with (suspected) ANCA vasculitis with pulmonary involvement (API)
1. Suspected or diagnosed with ANCA-associated vasculitis
2. (Suspected) pulmonary involvement attributable to vasculitis
3. Patients who undergo a bronchoalveolar lavage (BAL) for diagnostic purposes

SLE patients with renal involvement
1. SLE diagnosis according to the 2019 EULAR/ACR Classification Criteria18
2. Renal involvement attributable to SLE
3. History of ANA positivity

Exclusion criteria

Patients with ANCA-associated glomerulonephritis (AGN) and Patients with (suspected) ANCA vasculitis with pulmonary involvement
1. A history of drug-induced ANCA-associated vasculitis
2. Active infection as shown by microbiological analysis

Healthy controls and hemodialysis controls
1. Active infection as shown by microbiological analysis
2. A history of any auto-immune disease
3. Use of immunosuppressive medication

Infection controls
1. Other infection than pneumonia/urine tract infection
2. A history of any auto-immune disease
3. Use of immunosuppressive medication

SLE patients
1. A history of drug-induced SLE
2. Active infection as shown by microbiological analysis

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-11-2020
Enrollment:	103
Type:	Actual

Ethics review

Approved WMO Date:	11-09-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-11-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-06-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-10-2021
Application type:	Amendment
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

ID: 29001
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL74517.018.20
OMON	NL-OMON29001