The role of monocytes and macrophages in the development of ANCA vasculitis in the kidneys

Published: 14-09-2020
Last updated: 15-05-2024

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.

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

Summary

ID

NL-OMON29001

Source
NTR

Brief title
MOMA

Condition

- Autoimmune disorders

Synonym
ANCA vasculitis

Health condition

Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis

Research involving
Human

Sponsors and support

Primary sponsor: Amsterdam UMC
Source(s) of monetary or material Support: Nierstichting

Intervention

- Other intervention

Explanation

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

To relate HLA-DPB1*04:01 genotype, quality of life and fatigue measurements and clinical parameters (disease activity (BVAS, VDI), immunosuppressive medication) to macrophage phenotype (in vitro and in situ) and Tcell activation and migration.

Study description

Background summary

Rationale: 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. 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 population: We will include AGN patients (n=40), stratified by ANCA subtype (75% PR3- and 25% MPO-ANCA associated AGN) and by disease activity (40% active disease). Healthy controls (HC, n=20) will be recruited. To separate AGN-specific macrophage activation from SLE, infectious and hemodialysis mediated activation, SLE patients with renal involvement (n=10), patients with an acute infection (pneumonia/urine tract infection) (n=10) and patients on hemodialysis (n=10) will serve as disease controls. To compare the phenotype of pulmonary macrophages with monocyte-derived macrophages, patients with (suspected) ANCA vasculitis with pulmonary involvement (n=10) (API) who undergo a bronchoalveolar lavage (BAL) for diagnostic purposes will be included. Patients who undergo a nephrectomy for a renal cell carcinoma (n=3) and patients with SLE (n=3) will be used as controls for in situ single-cell RNA sequencing experiments. Main study parameters/endpoints: 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.

Study objective

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 design

Visit 1: all groups Visit 2: patients with ANCA-associated glomerulonephritis and ANCA patients with pulmonary involvement, healthy controls, SLE patients,

Contacts

Public

Amsterdam UMC
M.L. Hilhorst

Scientific
Amsterdam UMC
M.L. Hilhorst

Eligibility criteria

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

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 3. A history of any other auto-immune disease 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 phase:	N/A
Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown
Primary purpose:	Basic science

Recruitment

NL

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

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Approved WMO

Date:	11-09-2020
Application type:	First submission
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660

1100 DD Amsterdam

020 566 7389

mecamc@amsterdamumc.nl

Study registrations

Followed up by the following (possibly more current) registration

ID: 55167
Bron: ToetsingOnline
Titel:

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL8869
CCMO	NL74517.018.20
OMON	NL-OMON55167

Study results