The role of gutmicrobiota composition, epigenetics and autoimmunity in the development and treatment of vasculitis; the VASKIR biobank

Published: 17-05-2022
Last updated: 24-06-2025

Primary Objective: Primary: Gut microbiota (oral and fecal) and nasal microbiota composition in relation to autoimmunity status (antibodies (ANA, ANCA) and HLA subtype) and inflammatory functional assays as well as disease ...

Ethical review	Approved WMO
Status	Pending
Health condition type	Vascular infections and inflammations
Study type	Observational invasive

Summary

ID

NL-OMON51405

Source
ToetsingOnline

Brief title
GAVAS

Condition

- Vascular infections and inflammations
- Autoimmune disorders
- Nephropathies

Synonym
vasculitis; blood vessel inflammation

Research involving
Human

Sponsors and support

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

Intervention

- No intervention

Keyword: autoimmunity, microbiome, vasculitis

Explanation

N.a.

Outcome measures

Primary outcome

Primary: Gut microbiota (oral and fecal) and nasal microbiota composition in
relation to autoimmunity status (antibodies and HLA subtype) and circulating
immune cell (functional) assays in patients with an autoimmune disease potentially leading to vasculitis.

Secondary outcome

• Treatment efficacy (as determined by change in inflammatory parameters, time to relapse, disease-specific activity index)
• Questionnaires about abdominal complaints and antibiotics use during life
• Efficacy of medication in relation to microbiota changes as well as on circulating immune cells (flow cytometry and functional assays) and plasma metabolites
• HLA type by high resolution sequencing of circulating neutrophils; from the literature it is known that certain HLA high-risk alleles may act as an effect modifier on the association between microbiota and disease severity. Since carriership of certain HLA alleles is also associated with outcome of disease (16, 17), we will include this variable into statistical models to determine the association of HLA alleles, disease severity with microbiota and metabolites.
• Body composition as measured by impedance, with that the risk for developing corticosteroid related complications
• Pathophysiology and development of cardiovascular events (defined as: myocardial infarction, hospitalization for unstable angina, hemorrhagic and ischemic cerebrovascular event, transient ischemic attacks and arterial revascularization procedures) after 1, 5 and 10 years after inclusion.

Study description

Background summary

Relevance: In the Netherlands, 100-300/100.000 people have some form of autoimmune systemic vasculitis which includes all types of vasculitis as defined by the Chapel Hill classification (1). Large-vessel vasculitides (LVV) include giant cell arteritis (GCA) and Takayasu arteriitis. Small-vessel vasculitides (SVV) are mainly associated with anti-neutrophil cytoplasmic antibodies (ANCA) and include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic GPA (EGPA). Other types affecting different vessel sizes (also termed variable vessel vasculitis) are Behçet*s disease, IgA vasculitis (formerly known as Henoch-Schönlein purpura), polyarteriitis nodosa (PAN), vasculitis associated with systemic lupus erythematosus (SLE), vasculitis due to systemic sclerosis and Sjögren's disease. Despite a clear
improvement in outcome over the last decades and upcoming novel therapeutics (2), vasculitis is associated with considerable morbidity and mortality (3, 4). Improved survival coincides with an increased risk of side-effects from intensive long-term immunosuppression, resulting in a high incidence of infections. Better and structured follow-up of vasculitis patients is needed, to better categorize them on the road to patient tailored medical therapy.

Background: Autoimmunity is the hallmark of all types of vasculitis, and this process may originate from an immune response to gut microbiota. Indeed, the composition of gut microbiota was found to be altered in several studies including different types of vasculitis (5), but diagnostic and predictive values remain to be established. Nevertheless, molecular mimicry and microbiota driven antibodies are thought to play a role in vasculitis (6, 7). Activation of innate immunity by intestinal microbes may be critical for accelerating vasculitis by expanding both T-helper 1 (Th1) and T-helper 17 (Th17) cells in the small intestine (8-10). Another mechanism linking the microbiome to immunological tone are microbial metabolites (11) and subsequent epigenetic modification (12). While most microbiome research focused on bacteria, gut viruses (virome) and fungi (all present in fecal samples) are also implicated in development of vasculitis because of consequent T-cell activation and exhaustion (13). These parameters are influenced by the different types of treatment used (14).
Thus the association between the gut microbiome/virome, T-cell exhaustion and immuno-tolerance in autoimmune vasculitis constitutes an important knowledge gap withholding a therapeutic target that will be addressed in this prospective cohort study.

Study objective

Primary Objective: Primary: Gut microbiota (oral and fecal) and nasal microbiota composition in relation to autoimmunity status (antibodies (ANA, ANCA) and HLA subtype) and inflammatory functional assays as well as disease activity parameters in patients with autoimmune diseases potentially leading to vasculitis.

Secondary Objective:
Gut microbiota (oral and fecal) and nasal microbiota composition in relation to:
• Questionnaires about abdominal complaints (to rule out intercurrent

gastrointestinal infections), quality of life
• Efficacy of medication in relation to microbiota changes as well as on circulating immune cell panel (including T-cells, B-cells, neutrophils and monocytes measured by flow cytometry and functional assays) and plasma metabolites
• HLA type by high resolution sequencing
• DNA buffycoat (whole genome sequencing and epigenetics)

Study design

This will be a cross-sectional observational cohort study. This study is performed in the outpatient setting. Individuals with autoimmune diseases potentially causing vasculitis >18 years old will be invited to participate and included if eligible and willing to participate. A cross-sectional design is sufficient to establish whether individuals with vasculitis carry a distinct microbiome and whether these individuals have altered circulating immune-cell and/or (epi)genetic signature. Moreover, we aim to study whether changes in gut, nasal and oral microbiota composition and plasma metabolite profiles are associated with outcome and treatment efficacy.

Intervention

Niet van toepassing

Study burden and risks

On day 1, subjects will collect a urinary morning sample and a fecal sample. A nosal and oral swab will be collected. Furthermore, participants will fill in questionnaires and food diaries. The participants will be burdened by the discomfort associated with collecting and storing urine, fecal and nose and oral swab samples. Furthermore, the questionnaires inquire about the burden of complications, abdominal complaints and comorbidities. This may be distressing as the participant is reminded that they are at risk of developing these conditions. These data, however, also result in a thorough check-up of patients. On day 2 (visit to outpatient clinic for regular clinical care), participants will be asked for ablood sample taken during the blood drawn during usual care. Oral microbiome will be collected at different sites. Microbiome from tongue, hard palate and buccal mucosa will be collected with sterile sampling swabs. These sites will be rubbed for 5-10 seconds. If any bleeding occurs, the sample will be discharged. For nose swabs, after the patient has blown their nose, a cotton swab will be introduced in the nose 2cm and turned 2-3 times. Patients will undergo a fibroscan to measure extent of liver fibrosis, if any.
On day 3 (regular clinical care visit 1 month after any new treatment initiation (or dose increase because of relapse) fecal and plasma samples are collected again to study if treatment efficacy is related to changes in gut microbiota and plasma metabolites. We argue that the risk and discomfort associated with this study is similar to the yearly auto-immune disease check-up and justified in light of the potentially profound insights and novel treatments to be gained by studying the impact of the gut microbiome on autoimmunity status in (auto-immune diseases that could cause) vasculitis.

If explicitly agreed upon by the patient, after 1, 5 and 10 years after inclusion, research staff will ask participants about relapse rate, and whether cardiovascular events have occurred (i.e. myocardial infarction, hospitalization for unstable angina, hemorrhagic and ischemic cerebrovascular event, transient ischemic attacks and arterial revascularization procedures).

Contacts

Scientific
Amsterdam UMC
M.L. Hilhorst
Meibergdreef 9
Amsterdam 1105AZ
Netherlands
0205669111
Public
Amsterdam UMC
M.L. Hilhorst
Meibergdreef 9
Amsterdam 1105AZ
Netherlands
0205669111

Trial sites

Trial sites in the Netherlands

Amsterdam UMC
Target size: 500

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
• All individuals with a disease that could lead to vasculitis (amongst others: ANCA vasculitides, systemiuc lupus erythematodes (SLE), systemic sclerosis, Sjögren’s disease, IgA-nephropathy, polyarteritis nodosa (PAN), Behçet's disease), visiting the outpatient clinic of Amsterdam UMC region are potentially eligible if theyare >18 years old
• Disease diagnosis is made by clinician. Vasculitis subtype will be recorded along with the presence of auto-antibodies at time of diagnosis and during remission (where applicable, e.g., in the case of AAV)

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
• Active infection at the time of inclusion (not to influence immune-cell function)
• Unwillingness to donate feces, urine and/or blood
• Inability to provide informed consent based on cognitive function, language barrier or other reasons
• Absence of large bowel (i.e., colostomy)

Study design

Design

Study phase:	N/A
Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Other type of control
Primary purpose:	Other

Recruitment

NL
Recruitment status: Pending

Start date (anticipated):	01-11-2022
Enrollment:	500
Duration:	6 months (per patient)
Type:	Anticipated

Medical products/devices used

Product type:	N.a.

IPD sharing statement

Plan to share IPD: Yes

Plan description
N.a.

Ethics review

Approved WMO Date:	25-11-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-04-2025
Application type:	Amendment
Review commission:	METC Amsterdam

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	NL81464.018.22
CCMO	NL81464.018.22
Research portal	NL-007272