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

Published: 25-11-2022
Last updated: 07-04-2024

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...

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

Summary

ID

NL-OMON51405

Source
ToetsingOnline

Brief title
GAVAS

Condition

- Autoimmune disorders
- Nephropathies
- Vascular disorders NEC

Synonym
vasculitis; blood vessel inflammation

Research involving
Human

Sponsors and support

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

Intervention

Keyword: autoimmunity, microbiome, vasculitis

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 vasculitis patients

Secondary outcome

• Treatment efficacy (as determined by change in inflammatory parameters, time to relapse, BVAS (see below)

• Questionnaires about abdominal complaints, quality of life, antibiotics use during life

• Birmingham vasculitis activity score (BVAS), a validated score that measures the activity of several vasculitis diseases (16).

• 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

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from the literature it is known that certain HLA high-risk alleles may act as

an effect modifier on the association between microbiota and vasculitis severity. Since carriership of certain HLA alleles is also associated with outcome of disease (17, 18), we will include this variable into statistical models to determine the association of HLA alleles, disease severity with microbiota and metabolites.

• DNA buffycoat (whole genome sequencing and epigenetics)

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) and vasculitis due to systemic sclerosis. 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 LVV and SVV, 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).
Capillary microscopy is a standard noninvasive diagnostic tool for systemic sclerosis, with similar sensitivity and specificity as the ANA titer. Data on capillary architecture in other vasculitides is scarce, and it is unknown whether there is any diagnostic or prognostic value. The current study offers an opportunity to investigate this further. 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 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 of circulating neutrophils
• 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 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 and nasal microbiota composition and plasma metabolite profiles are associated with outcome and treatment efficacy.

Study burden and risks

This is an observational study without invasive measurements outside of a test

for which patients will be fasted. We will therefore record the following adverse events in the CRF if they occur:
• Hematoma after venous puncture, larger than 6cm
• Syncope

The CRU will monitor this study, and this study has been reported to the CRU (please see attached form).

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 to participate in this study, a subject must meet all of the following criteria:

• All individuals with vasculitis visiting the outpatient clinic of Amsterdam UMC region are potentially eligible if they are >18 years old
• Vasculitis 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 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):	01-11-2022
Enrollment:	500
Type:	Anticipated

Ethics review

Approved WMO Date:	25-11-2022
Application type:	First submission
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

No registrations found.

In other registers

Register	ID
CCMO	NL81464.018.22