VASFASS: Linking VASculopathy and Fibrosis with Auto-immunity in Systemic Sclerosis

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1. Define in detail how autoantibodies and changes in the B cell compartment correlate with different stages of clinical microvascular damage in SSc.2. Determine which soluble factors, including autoantibodies, in SSc-blood of clinically well-...

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

Summary

ID

NL-OMON54885

Source
ToetsingOnline

Brief title
VASFASS

Condition

- Autoimmune disorders
- Vascular disorders NEC

Synonym
Scleroderma

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Galapagos,Health Holland

Intervention

Keyword: Auto-antibodies, Auto-immunity, Endothelial cell activation, Systemic Sclerosis

Outcome measures

Primary outcome

Insight in clinical associations and functional roles of functional vascular autoantibodies in SSc. Identification of drugable targets that can interfere with endothelial cell damage and development of fibrosis in SSC using high-throughput in-vitro models with patient derived endothelial cells, fibroblasts and blood samples.

Secondary outcome

Not applicable.

Study description

Background summary

Systemic sclerosis (SSc) is a severe disease characterized by the triad of microangiopathy, dysregulated immune system and excessive fibrosis of skin and internal organs. To date no curative treatment options with acceptable safety profile are available. Immune dysregulation, characterized by presence of specific autoantibodies, and microangiopathy, resulting in Raynaud*s phenomenon, are among the earliest signs of the disease and predict further progression. Recently, autoantibodies that bind to G protein-coupled receptors including angiotensin II type 1 receptor (AT1R) and endothelin-1 type A receptor (ETaR) that target receptors on endothelial cells, have been described in SSc patients. Presence of these antibodies is associated with more severe disease and increased chance of severe vascular complications.
We hypothesize that SSc sera itself contain the factors that cause endothelial damage, and as such lead to vascular leakage, hypoxia and consequently tissue fibrosis. We hypothesize that the factors that cause endothelial cell dysfunction and damage are derived from dysregulated B cells and might

Study objective

1. Define in detail how autoantibodies and changes in the B cell compartment correlate with different stages of clinical microvascular damage in SSc.
2. Determine which soluble factors, including autoantibodies, in SSc-blood of clinically well-described SSc-patients contribute to endothelial damage in a micro-vessel-on-chip model in vitro.
3. Identify, using the microvessel model and a functional model, targets that can prevent endothelial cell damage
4. Characterize fibroblasts isolated from skin of patients with high risk for severe fibrotic complications (*active profibrotic disease*) and evaluate associations between clinical microvascular damage and proinflammatory fibroblast markers.

Study design

Interventional, prospective, single center study

Intervention

skin biopsy of affected and non-affected skin of SSc patients.

Study burden and risks

No major risks are associated with this study. Skin biopsies are easily mastered, quick and have a low incidence of infection, bleeding, non-healing or significant scarring. No direct benefit from participation is expected for this study. However, this project may deliver new drugable targets for SSc which is a chronic and devastating disease for which currently no good treatment options exist.

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

Main inclusion criteria:
In order to be eligible to participate in this study, a subject must meet all of the following criteria:
1. Diagnosis of systemic sclerosis according to ACR/ EULAR 2013 criteria or very early diagnosis of systemic sclerosis based on presence of antinuclear antibodies, and Raynaud*s phenomenon, and additionally presence of puffy fingers OR abnormal nailfold capillaroscopy (thus not fulfilling ACR/ EULAR 2013 criteria
2. Age >= 18 years
3. Disease duration: a. equal to or less than 24 months since the first non-Raynaud symptom, OR b. signs of active vasculopathy during the past 6 months including any one of the following: 1. new, painful pitting scars, 2.new digital ulcer or peripheral necrosis, 3. Newly diagnosed pulmonary arterial hypertension, 4. newly diagnosed scleroderma renal crisis.
4. Presence of Raynaud*s phenomenon
5. Signed informed consent

Additional inclusion criterium for skin biopsy:
1. Skin involvement proximal to the wrist or ankles

Exclusion criteria

Patients who have been treated with specific B cell depleting therapies (during the past 12 months) or with autologous stem cell transplantation (ever) will be excluded.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	26-04-2022
Enrollment:	200
Type:	Actual

Ethics review

Approved WMO

Date:	25-03-2021
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	NL71598.058.19

Study results

Date completed: 21-12-2023

Summary results
Trial ended prematurely