Tight control in the vascular endotype of systemic sclerosis.
Improving outcomes in pulmonary arterial hypertension associated with systemic sclerosis using personalized medicine, a predictive study.

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Specific objectives:* To analyse the predictive value of the presence of anti-ETaR, anti-AT1R and a reduction in capillary density, for the development of PAH in patients with SSc, alone and in combination.* To analyse whether anti-ETaR, anti-AT1R...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON44207

Source
ToetsingOnline

Brief title
Tight control in the vascular endotype of systemic sclerosis.

Condition

- Other condition
- Autoimmune disorders

Synonym
pulmonary arterial hypertension associated to systemic sclerosis

Health condition

pulmonale hypertensie

Research involving
Human

Sponsors and support

Primary sponsor: Radboudumc
Source(s) of monetary or material Support: Combinatie van unrestricted grant en aanvraag verstuurd voor reumafonds

Intervention

Keyword: Pulmonary hypertension, Systemic sclerosis, Vascular antibodies, Vascular endotype

Outcome measures

Primary outcome

Expected results and conclusions

We hypothesize that in patients with a vascular endotype of SSc both the

incidence of PAH and mortality due to PAH will be higher than in patients

without this endotype. More intense screening algorithms will be applicable for

these vascular endotype patients for early diagnosis and treatment. This will

shed new light on the screening of PAH in SSc with risk stratification and

appliance of personalized medicine and herewith early diagnosis of PAH, early

implementation of targeted treatment, improving survival and saving costs.

Secondary outcome

na

Study description

Background summary

Introduction
Systemic sclerosis (SSc) is a generalized auto-immune disease characterized by inflammation, micro-vasculopathy and fibrosis, affecting skin and internal organs. The primary cause of death in patients with SSc is interstitial lung disease, followed by pulmonary arterial hypertension (PAH) (1). PAH has a prevalence of 8-12% among SSc patients and is diagnosed by right heart catheterization. The 3 year survival rate of PAH associated with SSc (PAH-SSc) is estimated to be only 52%, despite the available targeted treatment (2). Survival benefits when treated with targeted therapy are the greatest in those diagnosed and treated in early stages of PAH (3). Screening programs, such as the DETECT algorithm, consist of clinical parameters, echocardiography, lung function with single-breath diffusion capacity for carbon monoxide (DLCO) and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, determined once a year. However, the results of these assessments are by definition abnormal in patients with PAH-SSc, and are therefore actual methods for diagnosing established PAH and not for early stages of PAH or PAH yet to develop. Therefore new diagnostic and prognostic biomarkers are needed to identify patient subsets that are likely to develop PAH and to benefit most from targeted therapy. If a high risk subset of patients is identified, personalized screenings methods can be applied to reach earlier diagnosis of PAH. Then, early treatment can be applied, and therewith improving the survival of this complication of SSc would be feasible.

Recently, two functional antibodies are identified to predict the development of PAH: anti-endothelin receptor type A (anti-ETaR) and anti-angiotensin II receptor type I antibodies (anti-AT1R) (4). However, validation in a large, prospective cohort is necessary for definitive proof of the value of these vascular biomarkers. Several small cross sectional nail fold capillary microscopic (NCM) studies showed that in PAH-SSc patients a significant decrease in capillary density is present compared to SSc patients without PAH and patients with idiopathic PAH (5, 6).

Hypothesis
We hypothesize that anti-endothelin receptor type A (anti-ETaR), anti-angiotensin II receptor type I antibodies (anti-AT1R), and a reduction in capillary density as seen with nailfold capillaroscopy (NCM) are biomarkers of a 'vascular endotype of disease' and as a consequence, that in combination they are predictive for the development of pulmonary arterial hypertension in patients with SSc. The use of these *vascular endotype* biomarkers to select SSc patients for more intensive PAH screening programs will allow more precise and earlier identification of PAH patients, improving PAH-SSc related survival.

Study objective

Specific objectives:
* To analyse the predictive value of the presence of anti-ETaR, anti-AT1R and a reduction in capillary density, for the development of PAH in patients with SSc, alone and in combination.
* To analyse whether anti-ETaR, anti-AT1R and a reduction in capillary density have a predictive value over and above sex, age, and clinical variables as in the DETECT algorithm.

Study design

Workplan
* A 3-year prospective, predictive study
* Patients with SSc fulfilling the ACR-EULAR classification criteria, with DLCO< 80% predicted and without PH, aiming to find 50 incident cases
* Clinical evaluation, questionnaires laboratory assessments, nailfold capillaroscopy en vascular receptor antibodies assessments every 3 months
* Pulmonary function tests and echocardiography every 6 months
* HRCT scan and/or right heart catheterization as clinical indicated following current guidelines
* Primary endpoint: diagnosis of PAH by right heart catheterization
* Secondary endpoints: survival of PAH-SSc, development of digital ulcers as symptom of vascular endotype of SSc, quality of life.

Study burden and risks

na

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

Fulfilling the ACR-Eular classification criteria of systemic sclerosis (15)
DLCO <80% of predicted
Age over 18 years

Exclusion criteria

Diagnosis of pulmonary hypertension
Current treatment with endothelin receptor antagonists or angiotensin blokkers
Cyclophosphamide treatment or autologous stem cell transplantation

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Will not start

Enrollment:	50
Type:	Anticipated

Ethics review

Approved WMO Date:	05-10-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	NL62650.091.17