Novel diagnostic approaches and markers for follow-up in systemic sclerosis

Published: 11-11-2013
Last updated: 24-04-2024

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

Summary

ID

NL-OMON45160

Source
ToetsingOnline

Brief title
Diagnosis and biomarkers in systemic sclerosis

Condition

- Autoimmune disorders

Synonym
scleroderma, systemic sclerosis

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Actelion Pharamaceuticals Nederland B.V.,Farmaceutisch bedrijf: Actelion

Intervention

Keyword: Biomarkers, Diagnostics, Nailfold capillaroscopy, Systemic sclerosis

Outcome measures

Primary outcome

Main study parameters include

a) levels of:

Connective tissue growth factor (CTGF)

TGF-beta responsive gene signature

N-terminal pro-peptide of type I (PINP) and type III

(PIIINP) collagen

C-terminal pro-peptide of type I collagen

cross-linked carboxyterminal telopeptide of type I collagen

C-terminal telopeptide of type I collagen

soluble intercellular adhesion molecule-1 (sICAM-1)

soluble vascular adhesion molecule 1 (sVCAM-1)

E-selectin

NT-proBNP

Uric acid

b) Presence (+ or -) of SSc specific autoantibody subtypes

Scl-70, CENP A, CENP B, RP11, RP155, Fibrillarin, NOR90,

Th/To, PM-Scl100, PM-Scl75, Ku, PDGFR, Ro-52

inflammatory parameters and interleukins

c) EUSTAR SSc Activity Score

The main endpoint is the correlation between the activity score (c) and presence and levels of markers as summarized under a and b.

Secondary outcome

Secondary endpoints relate to potential clinical significance of biomarkers in evaluating therapeutic efficacy. During follow-up and upon treatment levels and presence of markers will be evaluated and correlated with disease activity. In this way markers of treatment efficacy may be revealed.

Study description

Background summary

Fibrosis is a leading cause of morbidity and mortality in the Western World. The hallmark of fibrosis is abnormal and exaggerated fibroblast proliferation and deposition of extracellular matrix components leading to irreversible organ damage and dysfunction. Inflammatory diseases such as systemic sclerosis, pulmonary fibrosis, but also liver cirrhosis and myocardial infarction end up with fibrosis. This concerns also involvement of the pulmonary arterial vessels, leading to pulmonary arterial hypertension (PAH). PAH and pulmonary fibrosis have a very bad prognosis . Together responsible for 60% of the mortality in systemic sclerosis.
Systemic sclerosis is a complex multisystem autoimmune disease with a wide heterogeneity in phenotype and outcome. Apart from progressive fibrosis, pathologic processes in systemic sclerosis include immune system activation and vasculopathy.
Although recent ethiopathogenic advances have been made, systemic sclerosis remains one of the most complex autoimmune diseases in terms of identifying patients at risk of developing adverse outcomes, therapeutic management and establishing the therapeutic effects. Further insight in factors predicting disease severity and organ involvement may lead to earlier and organ-specific treatment and improves diagnostic follow-up.
The focus of the present study will be to determine factors that predict disease activity, severity and progression. This will be done through combining evaluation of laboratory parameters (including inflammatory markers) and estimation of vasculopathy by nailfold capillaroscopy. Moreover, we will evaluate blood flow and changes in flow in the hands of patients with systemic sclerosis as well as effects of treatment on this blood flow. Finally, we will identify factors that evaluate therapeutic efficacy and may be used as markers

for follow-up.
By determining factors that predict disease severity and give insight in (future) organ involvement follow-up of patients with systemic sclerosis could be further individualized and future treatment may be initiated in earlier stages based on the risk of development of certain organ damage.

Study objective

The main objective of the current study is to determine factors that are markers for disease activity, future progression and may be indicative for specific organ involvement. In the current project we will focus on the following objectives:

I) Determination of factors (blood abnormalities) that predict systemic sclerosis disease severity, organ involvement, and progression

II)Evaluation of correlations between disease severity, laboratory findings and nailfold capillaroscopy findings as well as blood flow analysis

III) Determination of factors that represent or evaluate therapy efficacy

Study design

Objective I (approx. 6 months):
When patients are diagnosed with systemic sclerosis it is of importance to determine which patients may develop early progressive fibrosis or are at risk for future pulmonary arterial hypertension. Currently available biomarkers show insufficient sensitivity and specificity in patient risk stratification. The ideal biomarkers predict future developments of relevant outcomes, are easily measurable and change with effective therapy. In the present study we will determine potential novel biomarkers for systemic sclerosis. Various biomarkers, as mentioned below, will be evaluated:

Connective tissue growth factor (CTGF)
TGF-beta responsive gene signature
N-terminal pro-peptide of type I (PINP) and type III (PIIINP) collagen
C-terminal pro-peptide of type I collagen markers of collagen formation
cross-linked carboxyterminal telopeptide of type I collagen
C-terminal telopeptide of type I collagen
soluble intercellular adhesion molecule-1 (sICAM-1)
soluble vascular adhesion molecule 1 (sVCAM-1) markers of vasculopathy
E-selectin
NT-proBNP
Uric acid markers of PAH
Auto-antibodies associated with systemic sclerosis as autoantibodies against Scl-70, CENP A, CENP B, RP11, RP155, Fibrillarin, NOR90, Th/To, PM-Scl100,

PM-Scl75, Ku, PDGFR, Ro-52
inflammatory parameters (including cell biology) and interleukins

In preliminary studies it was described that the above mentioned biomarkers were elevated in systemic sclerosis patients. Studies were all performed in small patient groups and the correlation with disease severity or progression has not been studied.
In the proposed study, we have the opportunity to include a large number of patients and their data. Due to the large study population (Dept. of Internal Medicine, Erasmus MC 60 patients, Dept. of Dermatology, Erasmus MC 20 patients) we might gain a significant insight into the relationship between expression of above mentioned markers and disease activity/severity.
Informed consent will be obtained from all patients included in our study and disease activity/severity will be well documented.
Disease activity will be evaluated and scored in all cases by estimation of the degree of skin fibrosis (performed by a dermatologist) scoring, pulmonary fibrosis (determined by computed tomography), pulmonary arterial hypertension (determined by echocardiography), kidney function (determined by creatinin levels in serum and urinary protein loss), diffusing capacity of the lung for carbonmonoxide (DCLO, evaluated by lung function tests) and using the EUSTAR Systemic Sclerosis Activity Score.

During follow-up of our patients determination of kidney function, DCLO and degree of skin fibrosis will be performed every 6 months.
Echocardiography will be repeated every 12 months after inclusion in our study.
Clinical findings at baseline and after 5 years will be correlated to the results obtained in our biomarker analysis in order to gain insight in the potential relation between biomarker profiles and disease severity.

If necessary skin biopsies will be taken by experienced dermatologists in order to obtain skin biopsies of good quality and from standardized sites of the human body
ELISA assays will be performed according to manufacturer*s protocol using the following kits: Human CTGF ELISA construction kit, Antigenix America Inc., RIA Kit for Human PINP, RIA Kit for Human PIIINP, ELISA Kit for human PICP, ELISA Kit for Human CTXI (all by Uscn Life Science Inc.), RayBio® sICAM-1 ELISA Kit, RayBiotech Inc., Quantikine® Human SVCAM-1 Immunoassay, R&D Systems Inc., Human sE-selectin ELISA Kit, Abnova Corporation.
Detection of autoantibodies using the EuroImmun Systemic Sclerosis Blot (detecting the above mentioned autoantibodies)
Cytokine analysis will be performed using a Cytokine Blot
TGF-beta responsive gene expression profile will be evaluated using RT-PCR after design of appropriate primers and probes

Objective II (total time span 6-9 months):
Nailfold capillaroscopy has recently been proven to be of significance in determining vasculopathy in systemic sclerosis. A typical systemic sclerosis

associated pattern is characterized by microhemorrhages, capillary loss, giant capillaries and ramifications. Until now, based on these observations, three patterns have been described, that enable stratification between *early*, *active* and *late* disease. These patterns have been found to correlate with disease severity. Using the capillaroscopic skin ulcer risk index (CSURI score) the risk of developing digital ulcers in systemic sclerosis patients can be predicted.
By performing nailfold capillaroscopy at different time points and correlate these outcomes with factors as described under objective I, we will try to characterize specific disease severity patterns in more detail.
Moreover we will incorporate questionnaires (Scleroderma Health Assessment Questionnaire (sHAQ), Cochin Scale determining hand disability and SF-36 determining patient health). We expect that we will also identify additional specific nailfold capillary patterns that enable improved patient risk stratification. Potentially, based on these scores, interventional approaches can be adjusted.

Set up:
1. Nailfold capillaroscopy will be performed on all systemic sclerosis patients from the department of Internal Medicine, Erasmus MC included in our study at different time points. First evaluation will be on study entrance and nailfold capillaroscopy will be repeated every three months. We will evaluate and score all single capillaries of digits two to four of both hands in order to generate a more accurate description of the nailfold capillary abnormalities.
2. Correlate findings under Objective I to findings obtained with nailfold capillaroscopy in order to more accurately estimate disease activity and predict progression.
3. Evaluate nailfold capillaroscopy findings before and after start of treatment to determine potential differences in capillary profiles (in relation to potential differences in biomarkers), that may be predictive for treatment responses. Final evaluation will be 12 months after initial start of immunosuppressive therapy

Laser Doppler imaging has recently been shown to effectively demonstrate blood flow restrictions in the hands of systemic sclerosis patients. In our outpatient clinics we will use this technique to monitor blood flow gradients in hands of patients with systemic sclerosis before and during treatment and evaluate potential improvement in this gradient. We will correlate the findings obtained under Objective I with Laser Doppler images in order to more accurately estimate disease activity.

Objective III (total time span of 18 months):
We will evaluate the correlation between the effects of treatment, as initiated based on disease severity and organ involvement, on the disease severity and serum levels of markers of collagen synthesis, vasculopathy, systemic sclerosis associated autoantibodies and other possible biomarkers that we identified under Objective I.

We will include the data on serum biomarker levels throughout disease progression or regression under therapy as identified under Objective I.

Set up:
1. Evaluation of therapy efficacy by determining the above mentioned disease activity parameters by experienced physicians
2. Evaluation of biomarker expression in patients sera
3. Correlations between improvement of disease activity with serum biomarker levels in stored patients sera collected from the different departments to estimate which biomarker in systemic sclerosis patients may be useful in follow-up of disease activity
4. Estimation of nailfold capillaroscopy and blood flow changes after treatment to provide a non-invasive tool for determination of therapy efficacy
5. Implementation of measurements of biomarkers in follow-up of systemic sclerosis patients, next to currently running measurements of for instance auto-antibodies

Study burden and risks

In a 5 years period patients with established systemic sclerosis are followed at the outpatient clinics of the department of Immunology accorinding to current follow-up protocols at our department for patients with systemic sclerosis.
During this periode, patients are asked to complete a set of 3 questionnaires on 3 different occassions, taking approximately 30 minutes per set of questionnaires.
Secondly, at regular blood drawing occassions an additional number of 4 tubes (34 ml in total) will be taken from these patients, which menas that an extra amount of 34 ml of blood will be drawn at 10 regular visits.
Based on these two interventions in the current study the burden for the included patients is very low, meaning a visit taking 30 minutes longer for 3 times in 5 years years. As the blood drawings are part of regular blood drawings no extra interventions are needed.
Additional risks therefore seem to be neglectable.

At current, there is no direct benefit for the included patients in the study. Based on the results of this study our patients may benefit in the future of optimized follow-up protocols and potentiaaly earlier start of organ-specifixc treatment, however at the moment this is just speculative.

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

18-80 yrs
diagnosis of scleroderma/systemic sclerosis according to the ECR criteria of 2013
Written informed consent

Exclusion criteria

Under age of 18 or above 80
Incapacitated

Study design

Design

Study type: Observational non invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	22-05-2014
Enrollment:	200
Type:	Actual

Ethics review

Approved WMO Date:	11-11-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-01-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	NL44419.078.13