The Clinical Efficacy And Subclinical Effects on arterial STIFFNESS of bosentan therapy added to usual care in patients with systemic sclerosis with digital ulcers.

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To investigate whether bosentan added to usual care improves arterial stiffness after 3 months as measured as the pulse wave velocity (PWV) of the medium and large arteries corrected for blood pressure changes in patients with SSc with digital...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON45095

Source
ToetsingOnline

Brief title
CEASE STIFFNESS

Condition

- Autoimmune disorders

Synonym
scleroderma, Systemic sclerosis

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Actelion Nederland,Actelion Pharmaceuticals

Intervention

Keyword: Arterial stiffness, Bosentan, Digital ulcera, Systemic sclerosis

Outcome measures

Primary outcome

Mean of right and left carotid-femoral arterial (i.e. aortic) Pulse Wave

Velocity (cfPWV)

Secondary outcome

* Right and left carotid-brachial and carotid-radial arterial PWV (cbPWV and

crPWV)

* Local PWV of the right and left radial (rPWV), brachial (bPWV), femoral

(fPWV), and common carotid artery (cPWV)

* Mean intima media thickness (IMT) of right and left radial, brachial,

femoral, and common carotid artery

* Nail-fold Capillary Microscopy and derived indices: Microangiopathy Evolution

Score (MES), Capillaroscopic Skin Ulcer Risk Index (CSURI) and Prognostic Index

for Digital Laesions (PILD)

* Blood flow in the hands, and in different regions of the hands (region of

interest (ROI) 1, ROI 2 and ROI 3), as measured by Laser Doppler Perfusion

Imaging (LDPI) at standardised ambient hand temperature.

* Skin Autofluorescence

* Mean number of new DUs per and time to healing of the cardinal ulcer

* Urine albumin/creatinine ratio (ACR)

* Plasma NT-proBNP and uric acid

* Serum levels of matrix metalloproteinases (MMP 3 and MMP 9), and tissue

inhibitors of metalloproteinases (TIMP)

* Systolic, diastolic, and mean arterial blood pressure of the brachial artery

* Modified Rodnan Skin Score (mRSS)

* Scleroderma Health Assessment Questionnaire (SHAQ), EuroQol EQ-5D, and SF-36

Study description

Background summary

Digital ischemia is a major problem in patients with Raynaud*s phenomenon (RP), especially in those with underlying connective tissue diseases (CTD) such as systemic sclerosis (SSc). SSc is hallmarked by microvascular disease which can be assessed by nailfold capillary microscopy (NCM) to identify specific capillary patterns. However, it appears that vascular damage is not restricted to the capillaries, but may also extend to more upstream hand and forearm arteries. This may not only be reflected by clinically relevant structural abnormalities such as obliteration, but also by decreases in arterial function. The best characterised in RP is the occurrence of vasospasms after cold exposure. However, evidence points out that major stiffening of the arteries also occurs, potentially exaggerating digital ischemia and other vascular complications in SSc. Based on published research it is hypothesized that the drug bosentan may improve vascular stiffness via different routes and thus to reduce the number and severity of digital ulcers.

Study objective

To investigate whether bosentan added to usual care improves arterial stiffness after 3 months as measured as the pulse wave velocity (PWV) of the medium and large arteries corrected for blood pressure changes in patients with SSc with digital ulcers (DU) compared to a healthy controle group.

Study design

Randomized, prospective, 3-arm parallel group, open-label, (bosentan vs. usual care only vs. no care), blinded endpoint (PROBE), intervention trial in 40

patients, and 20 healthy controls.

Intervention

Group 1: Usual care AND bosentan 62.5 mg twice daily, titrated to 125 mg twice daily after one month if tolerated (n=20)
Group 2: Usual care only (n=20)
Group 3: healthy controls, no care (n=20)

Study burden and risks

Bosentan is a registered product in the Netherlands. In this study, it will be used within its indication and not in combination with other products for which it has not been registered. Therefore no additional unknown uncertainties and increased overall risk are applicable for the investigational product. In the usual care group, treatment will not differ from clinical practice. To minimize the risk of patients not receiving the most appropriate treatment in the control group, regular visits and lab assessments are planned. Patients are allowed the start in with bosentan in the usual care group if indicated by the treating physician. The study will consist of one screening and three study visits. During the latter, patients clinical signs and symptoms will be assessed, vascular lab will be performed, blood will be drawn, and subjects be asked to fill in questionnaire, all of which will have a duration of no more than 2 hours per visits. In total 3x 24cc of blood will be collected, preferably in combination will routine lab assessments. These measures render the risks acceptable and the burden minimal for the subjects participating in the study.

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

SSc patients
* 18 years or older
* Systemic sclerosis based on the 2013 ACR/EULAR criteria
* Raynaud*s phenomenon (RP)
* A history of digital ulcer disease
* Assessable Pulse Wave Velocity (PWV) measurement at baseline
* Written informed consent;Healthy controls:
* 18 years or older
* Written informed consent

Exclusion criteria

SSc patients:
* Hypersensitivity to the active substance or to any of the excipients
* Moderate to severe hepatic impairment, i.e., Child-Pugh class B or C
* Baseline values of liver aminotransferases, i.e., aspartate aminotransferases (AST) and/or alanine aminotransferases (ALT), greater than 3 times the upper limit of normal
* Concomitant use of cyclosporine A
* Pregnancy
* Women of child-bearing potential who are not using reliable methods of contraception
* Significant peripheral vascular disease as the sole consequence of atherosclerotic disease due to for example diabetes, dyslipidemia, systemic hypertension, coagulopathy;Healthy controls:
* Comorbidities

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-06-2015
Enrollment:	60
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Tracleer
Generic name:	Bosentan
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	13-04-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-04-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO

Date:	12-06-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-10-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-08-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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
EudraCT	EUCTR2014-002796-28-NL
CCMO	NL49919.042.14