Mesenchymal stem cells for angiogenesis and neovascularisation in digital ulcers of systemic sclerosis

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This study has been transitioned to CTIS with ID 2024-515387-31-00 check the CTIS register for the current data. To investigate whether in patients with peripheral vascular complications related to SSc, intramuscular allogeneic BM-MSC therapy is...

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

Summary

ID

NL-OMON47582

Source
ToetsingOnline

Brief title
MANUS Trial

Condition

- Autoimmune disorders

Synonym
scleroderma, Systemic scleroderma

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: ZonMW

Intervention

Keyword: Clinical trial, Mesenchymal stem or stromal cells, Systemic sclerosis, Vasculopathy

Outcome measures

Primary outcome

The primary outcome is the toxicity of the treatment at 12 weeks after MSC administration, defined as

- Local toxicity, including signs of local inflammation (swelling, warmth, impairment of function), worsening of ulcers or new ulcers or hematomes after MSC administration

- 2. Other adverse events, graded according to the Common Terminology Criteria for Adverse Events.t.

Secondary outcome

A secondary outcome measure for safety is the incidence (at 12 weeks post treatment) of any treatment-related serious adverse events (SAE) defined as events leading to hospitalization, death, or persistent or significant disability.

Secondary outcome measures for efficacy are: pain and disability parameters; healing, time to healing and reduction of new ischemic digital ulcers; modified Rodnan skin score; Scleroderma Health Assessment Questionnaire (SHAQ) including visual analogue scales (VAS) for scleroderma-specific symptoms; Quality-of-life (SF-36, EuroQol (EQ-5D); Cochin hand function score. We will also evaluate changes in capillary morphology and architecture using capillaroscopy; biochemical parameters; markers for endothelial activation and injury, inflammation , oxidative stress, circulating endothelial cells and

hematopoietic and endothelial progenitor cells, cytokines and growth factors,

immunological responses. Follow-up visits will be scheduled at 48 hours and 2,

4, 8, 12, 24 and 52 weeks post-treatment.

Study description

Background summary

Systemic sclerosis (SSc) is an autoimmune disease characterized by fibrosis and vasculopathy. Clinical features of vasculopathy are common and severe in patients with SSc. Digital ischemia is a frequent manifestation, which may lead to digital ulcers or acrolysis and tissue loss, infection, gangrene, amputation and septicaemia. Despite recent advances in pharmacological treatments there is currently no way to promote ulcer healing. New treatments are urgently needed. Mesenchymal stem or stromal cells (MSC), because of their immunomodulatory and vasculoregenerative properties, may provide a novel therapy for peripheral ischemia in SSc. Allogeneic MSC therapy is attractive as it involves functionally competent MSC from healthy donors and may be used as *off-the-shelf* available treatment.

Study objective

This study has been transitioned to CTIS with ID 2024-515387-31-00 check the CTIS register for the current data.

To investigate whether in patients with peripheral vascular complications related to SSc, intramuscular allogeneic BM-MSC therapy is feasible, safe and potentially effective. We expect that the proposed trial will allow us to come to a go-no go decision to proceed with a large multicenter study with longer follow-up within 2 years. In this follow-up trial, we also intend to further elucidate the mechanism of action of MSCs.

Study design

A randomized double-blind, placebo-controlled clinical trial.

Intervention

Patients are randomised (1:1) to intramuscular injection (8 sites) of allogeneic BM-MSC (50*10^6) or placebo in the ischemic limb.

Study burden and risks

Subjects will be screened in a baseline visit, where they will be physically examined and blood samples will be taken (40mL). An appointment for the treatment will be made. Consequently, there are 7 follow-up visits. Follow-up visits include physical examination and documenting of the ulcers. Questionnaires will be administered at baseline and at visit 5, 6 and 7. During the trial, the patients are subjected to venepuncture five times during which 40mL blood will be taken. Skin biopsies will be taken twice. Capillaroscopy (a non painful exam) will be performed at five visits.
In previous trials allogeneic MSC administration was not associated with serious adverse events and are well tolerated.

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

- Age >18 years
- Established diagnosis of SSc according to criteria of the American College of Rheumatology (2013)
- At least one active digital ulcer (painful area, >2 mm in diameter with visible depth and loss of dermis) refractory to 5 days intravenous prostacyclines
Refractory to prostacyclins is defined as
* - Worsening of ulcer(s) within 1 month after prostacyclins iv
* - No improvement of ulcer(s) after 2 months after prostacyclins iv, as judged by the referring physician
* - Recurrence of exactly the same ulcer(s) (same location) within 3 months after prostacyclins iv, - Written informed consent

Exclusion criteria

- Ulcer with underlying calcinosis (ruled out by X-ray prior to screening/inclusion)
- History of neoplasm or malignancy in the past 10 years
- Pregnancy or unwillingness to use adequate contraception during study
- Serious known concomitant disease with life expectancy <1 year
- Uncontrolled hypertension
- Uncontrolled acute or chronic infection
- Follow-up impossible

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	06-10-2021
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cels allogenic

Ethics review

Approved WMO Date:	25-06-2015
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-07-2016
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-03-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-06-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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
EU-CTR	CTIS2024-515387-31-00
EudraCT	EUCTR2015-000168-32-NL
CCMO	NL51705.000.15