Randomized controlled trial to compare the effects of single versus repeated intracoronary application of autologous bone marrow-derived mononuclear cells on total and SHFM-predicted mortality in patients with chronic post-infarction heart failure;REpetitive Progenitor cEll therapy in Advanced chronic hearT failure (REPEAT trial)

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The current randomized controlled trial should investigatewhether- 2 sequential intracoronary BM-MNC applications are associated with a lower mortality than oneintracoronary BM-MNC application- 2 intracoronary treatments with BM-MNC are associated...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Heart failures
Study type	Interventional

Summary

ID

NL-OMON47617

Source
ToetsingOnline

Brief title
REPEAT

Condition

- Heart failures

Synonym
Heart failure

Research involving
Human

Sponsors and support

Primary sponsor: Goethe University Frankfurt
Source(s) of monetary or material Support: Ministerie van OC&W,Goethe University Frankfurt

Intervention

Keyword: Bone marrow-derived mononuclear cells, Chronic, Heart failure, Old myocardial infarction

Outcome measures

Primary outcome

2-year total mortality is significantly lower in patients receiving 2 repeated

intracoronary applications of autologous bone marrow-derived progenitor cells

(t2c001) compared to patients receiving 1 intracoronary application of

autologous bone marrow-derived progenitor cells (t2c001).

Secondary outcome

In patients receiving 2 repeated intracoronary applications of autologous bone

marrow-derived

cells (t2c001), the observed mortality is significantly lower than the

SHFM-predicted mortality

at 2-year follow-up.

Comparison between the 2 treatment groups at 2-year and 5-year follow-up

* Cardiac mortality, cardiovascular mortality

* Rehospitalisation for heart failure

* Ischemic cardiac events (STEMI, NSTEMI, ACS)

* Coronary revascularisations (PCI / CABG)

* Heart transplantation, Assist-device implantation

* New resynchronization therapy, ICD implantation

* NYHA-Status, NT-proBNP serum levels

* Minnesota Living with Heart Failure Questionnaire

* Prespecified combined clinical endpoints:

o Death and rehospitalisation for heart failure

o Cardiac Death and rehospitalisation for heart failure

o Cardiac and Cardiovascular Death and rehospitalisation for heart failure

o Death and myocardial infarction

o Death and myocardial infarction and rehospitalisation for heart failure

o Death and any cardiovascular event

All in-hospital events (during hospitalization for cell therapy)

* Life-threatening arrhythmias (sustained ventricular tachycardia; ventricular fibrillation and cardiopulmonary resuscitation)

* Safety of intracoronary application of autologous bone marrow-derived cells (t2c001)

(procedural complications, adverse events at 30 days, SAEs at 4 months after each cell

application)

* Any new malignant disease within 5 years

* Bleeding events within 30 days after intracoronary cell application

Study description

Background summary

Patients with symptomatic chronic post-infarction heart failure under full dose conventional medical
and device treatment including resynchronization therapy frequently suffer from repeated
rehospitalisations for heart failure, and a high mortality rate. Whereas heart transplantation may be
considered as option for patients below the age of 65, this alternative is no possibility for the majority
of elderly patients with symptomatic heart failure. Moreover, heart transplantation is significantly
limited through the non-availability of donor organs. Thus, the situation is unsatisfying for the patients
as well as for the treating physicians.
In these patients, the application of bone marrow-derived progenitor cells is a novel treatment option.
Data of our own non-randomised studies suggest that BM-MNC application reduces serum levels of
NT-proBNP. In addition, the survival of patients treated with intracoronary infusion of BM-MNC was
better than the survival predicted by the established SHFM model. This effect was entirely driven by
patients receiving two sequential intracoronary treatments. However, these data were obtained from a
non-randomised registry, and, therefore, the current randomized controlled trial should investigate
whether
- 2 sequential intracoronary BM-MNC applications are associated with a lower mortality than one
intracoronary BM-MNC application
- 2 intracoronary treatments with BM-MNC are associated with a better survival than the survival
predicted with the SHFM model.

Study objective

The current randomized controlled trial should investigate
whether
- 2 sequential intracoronary BM-MNC applications are associated with a lower mortality than one
intracoronary BM-MNC application
- 2 intracoronary treatments with BM-MNC are associated with a better survival than the survival
predicted with the SHFM model.

Study design

Randomized controlled open-label trial.

Treatment group 1:
Single intracoronary application of autologous bone marrow-derived progenitor cells (t2c001) into open infarct-related vessel or bypass (n=334)

Treatment group 2:
2 repeated intracoronary applications of autologous bone marrow-derived progenitor cells (t2c001) into open the same infarct-related vessel or bypass (n=334), time interval between first and second treatment 4 months

Primary outcome: mortality

Intervention

Treatment group 1:
Single intracoronary application of autologous bone marrow-derived progenitor cells (t2c001) into open infarct-related vessel or bypass (n=334)

Treatment group 2:
2 repeated intracoronary applications of autologous bone marrow-derived progenitor cells (t2c001) into open the same infarct-related vessel or bypass (n=334), time interval between first and second treatment 4 months

Study burden and risks

The patients have the following additional investigations
* One or two cardiac catheterizations with 4 months difference
* One or two bone marrow aspiration(s) under local anaesthesia
* Routine investigations like physical examination and ECG
* 1 transthoracic ultrasound examination of the heart at baseline
* 7 to 8 times blood testing (ca. 30 ml each)

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

• Previous myocardial infarction at least 3 months ago, open infarct vessel or bypass
• Left ventricular ejection fraction (LVEF) <= 45% on echocardiography
• Stable chronic heart failure NYHA class II to III under constant (4 weeks) evidence-based optimal medical treatment
• age > 18 and expected to survive > 1 year
• written informed consent
• women of childbearing age: negative pregnancy test; effective contraception for the first 8 months in the trial

Exclusion criteria

• Non-ischemic cardiomyopathy
• Necessity for revascularization in other vessel than the infarct vessel at the time of study therapy
• Hemodynamic relevant severe valvular disease with indication for operative / interventional revision
• Heart failure with preserved ejection fraction (diastolic heart failure), LVEF > 45%
• Unstable Angina
• Severe peripheral artery occlusive disease (>= Fontaine stadium III)
• Active infection (C-reactive protein > 10 mg/dl), any chronic inflammatory disease
• Neoplastic disease without documented remission in the last 5 years
• Stroke <= 3 months
• Impaired renal function (Serum creatinine > 2,5 mg/dl) at the time of study inclusion
• Relevant liver disease (GOT > 2x upper normal limit, spontaneous INR > 1,5).
• Diseases of hematopoetic system, anemia (Hemoglobin < 8.5 mg/dl), thrombocytopenia < 100.000/µl)
• Splenomegaly
• Allergy or intolerance of clopidogrel, prasugrel, ticagrelor, heparin, bivalirudin
• History of bleeding disorder
• gastrointestinal bleeding <= 3 months
• major surgery or trauma <= 3 months
• Uncontrolled hypertension
• Pregnancy, lactation period
• mental retardation
• previous cardiac cell therapy within last 12 months
• Participation in another clinical trial <= 30 days

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial

Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	22-02-2016
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cells autologous

Ethics review

Approved WMO Date:	13-11-2015
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-12-2015
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-08-2019
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
EudraCT	EUCTR2011-000595-33-NL
CCMO	NL52576.000.15