Autologous bone marrow-derived mononuclear cells for therapeutic arteriogenesis in patients with limb ischemia
A double blind placebo controlled study in diabetic and non-diabetic patients

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To validate and extend findings from the TACT sytudy group as well as our own preliminary data in a randomized, placebo controlled study in patients with and without diabetes.

Ethical review	Approved WMO
Status	Pending
Health condition type	Arteriosclerosis, stenosis, vascular insufficiency and necrosis
Study type	Interventional

Summary

ID

NL-OMON37216

Source
ToetsingOnline

Brief title
Autologous bone marrow for peripheral artery disease.

Condition

- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
claudication

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Bone marrow derived mononuclear cells, Cell therapy, Claudication, Critical Limb Ischemia

Outcome measures

Primary outcome

Primary endpoints are pain free walking distance (Fontaine IIb/III), and limb

salvage/wound healing (Fontaine IV) at t=6 months.

Secondary outcome

Secondary endpoints include quality of life (RAND-36), walking impairment

score, pain scores, ABI at t=3, 6 and 12 months, Limb salvage/wound healing at

t=12 months as well as pain free walking distance at t=3 and 12 months. Upon

reaching the primary endpoint (t=6 months), the study will commence as an open

study. Patients in the placebo arm will be offered their frozen bone marrow.

Results of this intervention will be analyzed separately.

Study description

Background summary

Peripheral arterial occlusive disease (PAD) is a common condition with an age-adjusted prevalence of approximately 12% in the older population. The prevalence of PAD increases with age and an estimated 20% of the population over 70 years is affected. The by far most common symptomatic manifestation of PAD is mild to moderate claudication which has an age adjusted prevalence of 4.5% in the adult population, but prevalence rapidly increases with age, resulting in a prevalence rate of over 20% in the population aged 75 years and older. Owing to the formation of an adequate collateral network, the general

course of claudication is mild, and in the majority of patients symptoms resolve spontaneously or stabilize with modest impairments in ADL activities. However, in one quarter of the patients the disease has a less favorable course and progression of PAD ultimately leads to disabling claudication and critical leg ischemia, characterized by severe rest-pain and ischemic gangrene. The greater part of these patients may benefit from intervention procedure(s) (such as angioplasty and bypass operations) restoring blood supply to the ischemic area. Unfortunately, in a substantial proportion of patients (i.e. patients with diabetes mellitus(1) or patients requiring distal repair in the absence of an adequate vein graft) the prospects of intervention are notably poor, and in patients with small vessel disease and occlusion of the tibial arteries intervention may even be impossible. Prognosis for these patients in terms of quality of life, life expectancy and costs is poor and these patients can only be treated by a below- or above knee amputation (currently: ±1000/year in The Netherlands).
Advances in the field of vascular biology have led to concept of stimulation of collateral formation (or arteriogenesis) in situations in which revascularization procedures have failed or were not possible. The process of arteriogenesis is not fully understood but it is now conceived that increased sheer stress and overstretching of pre-existing interconnecting arterioles lead to endothelial cell activation and up-regulation of adhesion molecules. Mononuclear cells adhere to the activated vascular wall, transmigrate into peri-vascular space and become activated. This process is further amplified by a perpetual cycle through release of proinflammatory cytokines from activated monocytes and macrophages. Under the influence of a myriad of released growth factors, cytokines and possibly bone marrow-derived stem cells the arteriole undergoes extensive remodeling, which ultimately results in formation of an artery-like musclized conduit which,
compared to its original size, has increased approximate 40-fold in diameter.(2) The putative pivotal role of monocytes and macrophages in the process of arteriogenesis led to the hypothesis that transplantation of BM-MNC may argument collateral formation in cases where collateral formation is absent or has failed. This concept was confirmed in several animal models of limb ischemia,(3,4) which ultimately compiled into a clinical phase I-II study by the TACT group, published in the Lancet.(5) In this study, Tateishi and colleagues showed that local injection of BM-MNC in the gastrocnemius muscle of the ischemic leg was feasible and safe, significantly improved pain free walking distance, Brachial-Ankle Index, transcutaneous oxygen tension and reduced pain scores during a 24 week follow up.
Although the beneficial effects

Study objective

To validate and extend findings from the TACT sytudy group as well as our own preliminary data in a randomized, placebo controlled study in patients with and without diabetes.

Study design

A single center, randomized placebo controlled study, in patients with disabling claudication who are not amendable for conventional treatment

Intervention

Bone marrow will be harvested from the iliac crest (700-800 ml) and the BM-MNC concentrated to a final volume of 40 mL (average total cell count 1.5-6.0 109 cells). Patients in the placebo group will receive diluted erythrocytes (hematocrit 5%). This preparation is visually indistinguishable from BM-MNC concentrate. BM-MNC from the placebo-treated patients will be frozen for later use (see further). Remaining erythrocytes will be returned to the patients.
As results of our preliminary study indicate that exclusive intra muscular delivery is equally effective as combined intra arterial/intra muscular delivery, intra muscular delivery (40 injections in a 3X3 cm grid, gastrocnemius muscle) will be used as mode of delivery in this study for practical reasons.
Bone marrow derived mononuclear cells from placebo treated patients will be frozen and available to the patients upon reaching the primary end-point (t=6 months or eminent amputation).

Study burden and risks

Harvesting of bone marrow and the intramuscular injections are associated with significant discomfort, yet application of local-regional anesthesia during the whole procedere has significantly reduce the burden to the patient. Volume shiftst during bone marrow may result in cardiac problems, for this reason patients at risk will remain under close cardiac supervision .

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

Patients with persistent (>3 months, despite optimal treatment) disabling claudication or with critical leg ischemia (Fontaine's stages IIb-IV or Rutherford's categories 3-6) without adequate options for improvements by PTA or reconstructive surgery will be included in the study.

Exclusion criteria

candidates for angioplasty or bypass procedures
-inability to undergo bone marrow harvesting
-any condition in the affected limb that is anticipated to require surgical intervention in the first weeks after BM-MNC treatment

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-09-2006
Enrollment:	100
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cells autologous

Ethics review

Approved WMO Date:	08-02-2007
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-05-2011
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	EUCTR2006-002191-17-NL
CCMO	NL12343.000.06