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Autologous bone marrow cells in patients with critical limb ischemia

Submission date	Recruitment status	[_] Prospectively registered
23/07/2016	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
26/07/2016	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
18/07/2017	Circulatory System	

Plain English summary of protocol

Background and study aims

Atherosclerosis is a serious disease where a fatty substance, called plaque, buildsup in the arteries. Over time, plaque causes hardening and narrowing of the arteries, which leads to reduced flow of blood through the blood vessels. Over time this can cause the main arteries in the legs become narrowed. As the arteries become narrower, patients begin the feel pain even when at rest and are at severe risk of developing ulcers or gangrene (critical limb ischaemia). At this point, patients often undergo surgery to restore blood flow, to prevent the limb from dying and having to be amputated (cut off). If this surgery fails or the patient is not a suitable candidate for it, then treatment options for CLI are very limited. About 40% of these high-risk patients will require amputation within 6 months of the initial diagnosis and around 20% will die. Several studies show that the use of autologous bone-marrow cells (stem cells taken from a patient's own bone marrow) can improve circulation and help deliver oxygen to the body's tissues but encouraging growth of new blood vessels, preventing the need or amputation. Currently, the best way of delivering these bone-marrow cell (BMC) products is unknown. The aim of this study is to compare the effectiveness of stem cell therapy treatment for CLI when BMC products are injected directly into the arteries (intraarticular) or directly into the muscles (intramuscular).

Who can participate?

Adults with critical limb ischemia with related wounds (ulcers or gangrene) who are not suitable to surgery to widen blood vessels or divert around blockages.

What does the study involve?

All included patients receive stem cell therapy, but are randomly allocated to receive the injections of stem cells one of two ways. Bone marrow is taken using a large needle into the hip bones under analgosedation (pain and consciousness reduction, but no anesthesia). The bone marrow is then processed to provide 40 ml of bone marrow-rich stem cell product. Immediately after this, BMCs are given to patients by intramuscular (IM) (group A) or intraarterial (IA) (group B) injection. In group A, 40 mL of BMCs concentrate is administered under analgosedation by 20-40 injections into the muscles of the affected limb along the arteries in the thigh. In group B, IA injection of 40 mL of BMCs concentrate is applied through the skin via the common femoral artery (main leg artery) in the groin area under local anesthesia (numbing) at the place that the

artery is blocked on the affected limb using catheter (thin, flexible tube). The procedures for both groups last for approximately one hour. Participants are then followed up after 12 months to find out whether they have had to had an amputation and how well the wounds have healed.

What are the possible benefits and risks of participating?
Participants benefit from receiving stem cell treatment, which could help to improve there condition. When bone marrow is taken, there is a small risk of anemia (low red blood cell count) however in patients who have a normal red cell count before the procedure, this will not be significant. For the intramuscular injections, there is a theroetical risk of swelling (inflammation) but this will be avoided by not injecting the stem cells into wounds that are already inflamed. For the intraarterial injection, there is a small risk of blood clot or arterial pseudoaneurysm formation at the puncture site (blood clot that forms because of a leaking artery).

Where is the study run from?
National Institute of Heart and Vascular Diseases, Bratislava (Slovakia)

When is study starting and how long is it expected to run for?
June 2009 to June 2013

Who is funding the study?
European Regional Development Fund (Slovakia)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
24209

Study information

Scientific Title
Transplantation of autologous bone marrow cells in patients with no-option critical limb ischemia

Acronym
TABU

Study objectives
1. There is no difference in therapeutic effect between intramuscular verzus intraarterial mode of application of bone-marrow stem cell product
2. Degree of local limb inflammation and advance limb ischemia are negative predictors of effects of cell therapy

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethical Committee of National Institute of Heart and Vascular Diseases (Slovakia), 07/09/2009, ref: 24209

Study design
Single-centre randomised parallel trial

Primary study design
Interventional

Secondary study design
Randomised parallel trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Critical limb ischemia

Interventions
Participants are randomised into two groups by computer randomization program (local IM BMCs administration versus selective IA infusion, 1:1) with equal sex distribution and equal distribution of patients with diabetes in both groups.

Method of BMC isolation – both study arms: Isolation of stem cells is realized under analgosedation with propofol. A total of 240 mL of bone marrow from both posterior iliac crests is harvested using a standard disposable needle for bone-marrow aspiration. Bone-marrow aspirate was processed using a SmartPreP2 Bone Marrow Aspirate Concentrate System (Harvest, Plymouth, MA, USA), which uses gradient density centrifugation to provide 40 mL of bone marrow-rich product for all blood elements within 15 minutes.

Immediately after stem cells harvest and centrifugation, bone marrow cell (MBC) product is administered either intramuscularly (Group A) or intraarterially (group B).

Group A: Immediately after the harvesting and centrifugation of stem cells, in group A, 40 mL of BMCs is administrates under analgosedation with propofol by deep injections with a 23-G needle into the muscles of the affected limb along the crural arteries, with each injection being approximately 1 mL.

Group B: Intraarterial injection (IA) injection of 40 mL of BMCs is realized from a percutaneous retrograde contralateral femoral approach or antegrade femoral approach under local anesthesia at the site of arterial occlusion of the affected limb using a 4-F catheter at 800 mL/h.

The length of procedure in both groups is approximately one hour.

Patients are discharged the day after the procedure on dual antiplatelet therapy (aspirin and clopidogrel) and statin therapy. All patients receive conventional wound care during follow-up of 12 months.

Intervention Type
Procedure/Surgery

Primary outcome measure
Combined end-point of limb salvage and wound healing is measured at 12 months. Wound characteristics are documented by digital photography. Wound healing is evaluated by two independent physicians.

Secondary outcome measures
1. Mortality is assessed at 12 months follow-up. In case of absence of patients at regular follow-up control, the family of patient is contacted.
2. Amputation free survival is measured by clinical assessment at 12 months.
3. Major limb amputation rate is measured by clinical assessment at 12 months.
4. Limb perfusion is determined by measuring transcutaneous oxygen pressure (tcpO2) of the affected limb at baseline, 6 months, and 12 months. TcpO2 is measured using a TCM400 Mk2 monitor (Radiometer Medical ApS, Copenhagen, Denmark), at the forefoot in the supine position with an electrode temperature of 44°C.
5. Severity of limb ischemia is determined using the Rutherford classification at baseline, 6 months, and 12 months.
6. Severity of limb ischemia is determined using the ankle brachial index (ABI) assessment at baseline, 6 months, and 12 months. Measurement of the resting ankle–brachial index (ABI) is realized according to validated standards. It is calculated as the quotient of the highest ankle pressure and highest brachial systolic blood pressure (normal values, 0.95–1.2).
7. Pain scale is measured using a visual analog scale (VAS) graded form 0 to 10, at baseline, 6 months, and 12 months
8. Quality of life at 6 months and 12 months after BMC application is assessed by the EuroQol

questionnaire. Using a VAS, patients rate their overall health status from 0 (“worst”) to 100 (“best”) imaginable health.
9. Wound size is measured in cm2 at baseline, 6 months, and 12 months. Wound characteristics are documented by digital photography. Wound healing is evaluated by two independent physicians.

Overall study start date
01/06/2009

Completion date
01/06/2013

Eligibility

Key inclusion criteria
1. Patients over 18 years of age
2. With ischemic skin lesions (ulcers or gangrene) with a Critical limb ischemia Rutherford category of 5 or 6 according to the TransAtlantic InterSociety Consensus (TASC) classification (minor or major tissue loss)
3. Critical limb ischemia defined by ankle–brachial index ≤0.4, or ankle systolic pressure <50 mmHg, or toe systolic pressure <30 mmHg, or transcutaneous oxygen pressure (tcpO2) <30 mmHg
4. No option for endovascular or surgical revascularization assessed by a vascular surgeon and interventionalist
5. Failed revascularization defined as no change of clinical status with the best standard care 4 weeks after endovascular or surgical revascularization

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
62

Key exclusion criteria
1. Life expectancy <6 months
2. Evidence of malignancy during last 5 years
3. Proliferative retinopathy
4. Critical coronary artery disease or unstable angina pectoris
5. End-stage kidney disease and patient on dialysis
6. Bone-marrow disease (e.g., myelodysplastic syndrome, severe anemia, leukopenia, thrombocytopenia)

Date of first enrolment
01/10/2009

Date of final enrolment
01/06/2012

Locations

Countries of recruitment
Slovakia

Study participating centre
National Institute of Heart and Vascular Diseases
Pod Krasnou horkou 1
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Sponsor information

Organisation
National Institute of Heart and Vascular Diseases

Sponsor details
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Sponsor type
Hospital/treatment centre

ROR
https://ror.org/00gktjq65

Funder(s)

Funder type
Government

Funder Name
European Regional Development Fund

Results and Publications

Publication and dissemination plan
The manuscript with results of the study was submitted for consideration of publication to the Stem Cell Research and Therapy. This journal is interested in accepting it for publication after minor revision – registration of the study retrospectively in publicly available registries.

Intention to publish date
31/12/2016

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	17/08/2016		Yes	No
Results article	results	12/07/2017		Yes	No