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Clinical trial for the treatment of severe limb ischaemia by implantation of cultured immature red cells developed from small amount of bone marrow of the patient

Submission date 28/11/2007	**Recruitment status** No longer recruiting	[_] Prospectively registered [_] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 18/12/2007	**Overall study status** Completed	
Last Edited 12/04/2021	**Condition category** Circulatory System	

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
NH18-004

Study information

Scientific Title
Phase I/II clinical study of angiogenesis by Ex-Vivo Expanded Erythroblast Transplantation (Autologous) (EVEETA) for the treatment of patients with chronic severe limb ischaemia

Acronym
EVEETA study

Study objectives
Bone Marrow cell Implantation (BMI) has been utilised to treat patients with limb and heart ischaemia. However the angiogenic mechanism was not known. We have found that immature erythroid and monocytic cells included in the implanted bone marrow cooperatively induce angiogenesis via cell-cell interaction and the production of angiogenic growth factors. We then developed culture system of hematopoietic stem cells to expand ex vivo of immature erythroid and monocytic cells in human as well as mouse. Implantation of the ex vivo expanded cells from mouse bone marrow strikingly induced angiogenesis in ischemic lower limb of mice.

The present project has been planned to treat patients with severe limb ischemia by implantation of ex vivo expanded autologous bone marrow cells. Collection of 500 to 1,000 ml of bone marrow from a patient has been required for BMI, while 20 ml of bone marrow is enough for EVEETA.

Ethics approval required
Old ethics approval format

Ethics approval(s)
EVEETA Study, Version 1 was approved by:
1. Ethics Committee of Niigata University Medical School on the 24th May 2006 (ref: 448)
2. Institutional Review Board (IRB) for the Clinical Trials of Pharmaceutical Agents and Medical Instruments, Niigata University Medical and Dental Hospital on the 2nd August 2006 (ref: NH18-004)

EVEETA Study, Version 2 was approved by the Institutional Review Board (IRB) for the Clinical Trials of Pharmaceutical Agents and Medical Instruments, Niigata University Medical and Dental Hospital on the 27th November 2007 (ref: NH18-004)

Study design
Phase I/II study, open-labelled, non-randomised, single arm, single-centre trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Severe peripheral arterial disease including arteriosclerosis obliterans, Buerger disease and arteritis

Interventions

1. Autologous Bone Marrow Collection:
20 ml of bone marrow is collected from iliac crest under local anaesthesia 14 days before the implantation.

2. Ex Vivo Expansion Culture:
All procedures are enforced by exclusive technical exparts along the approved protocols in GMP-grade Cell Processing Room established in Bioscience Medical Research Center, Niigata University Medical and Dental Hospital. Mononuclear cells separated from the bone marrow are incubated in a suspension culture in the presence of rh Flt-ligand, rh SCF, rh Thrombopoietin, and culture supplements for 7 days to expand myeloid progenitors.

Harvested and washed cells are further cultured in the presence of rh SCF, rh IGF-I, rh Erythropoietin, and culture supplements for additional 7 days to expand immature erythroblasts and macrophages.

3. Preparation for implant:
Cultured cells are harvested and washed. The cells are resuspended in 50 ml of platelet concentrate supplemented with 6,000 IU of erythropoietin.

4. Treatment:
Aliquots of the 50 ml of cell suspension are intramuscularly injected in 100 points of the ischaemic limb. Daily intramuscular injection of rh erythropoietin in the same loci follows from the next day for consecutive 4 days.

Intervention Type
Other

Phase
Phase I/II

Primary outcome(s)
Efficacy evaluation: improvement in:
1. Ankle-Brachial Index (ABI) (1 month of implantation)
2. Transcutaneous Oxygen pressure (TcO2) (1 month)
3. Rest pain

Safety evaluation:
1. Adverse effects caused by the implanted cells including teratoma, ossification, etc.
2. Adverse effects caysed by erythropoietin including polycythemia, hypertension, pure red cell aplasia, thrombosis in heart/lung/brain, etc.
3. Adverse effects caused by possible residual components used as supplements for cell culture including allergy, serum sickness, infections, etc.
4. Common adverse effects caused by drug administration stated in National Cancer Institute Common Toxicity Criteria (NCI-CTC)

Key secondary outcome(s))
1. Improvement in ABI (6, 12, 18 and 24 month of implantation) and Transcutaneous Oxygen pressure (TcO2) (6, 12, 18 and 24 months)
2. Improvement in subjective symptoms: Visual Analogue Scale (VAS) in 1, 6, 12, 18 and 24 months of implantation
3. Improvement in limb ulceration in 1, 6, 12, 18 and 24 months of implantation

4. Elongation in range of pain-free walking in 1, 6, 12, 18 and 24 months of implantation
5. The requirement of analgesic in 1, 6, 12, 18 and 24 months of implantation
6. Manifestation of new collaterals evaluated by angiography in 1 month of implantation

Completion date
30/11/2011

Eligibility

Key inclusion criteria
1. Peripheral Arterial Disease (PAD) including Arteriosclerosis Obliterans (ASO), Buerger disease, and arteritis associated with collagen diseases
2. Fontaines stage: IIb, III, and IV
3. Chronic limb ischaemia, including rest pain, non-healing ischaemic ulcers, or both, and were not candidates for non-surgical or surgical revascularisation
4. Age: greater than 20 or less than 80 years
5. World Health Organization (WHO) performance status: 0 to 3

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Key exclusion criteria
1. Patients with the expected rest of their life less than 1 year
2. Patients with drug dependence during the past 3 months
3. Patients with malignant evidence of malignant disorder during the past 5 years
4. Patients with poorly controlled diabetes mellitus accompanied with proliferative retinopathy
5. Patients with significant coronary stenosis
6. Pregnant or possibly pregnant females
7. Patients with acute myocardial infarction, unstable angina, myocarditis, or cerebral infarction during the past 1 month
8. Patients with active infection including Treponema pallidum
9. Patients with positive test for Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV)
10. Patients with history of allergy for antibiotics or iodo

Date of first enrolment
28/11/2007

Date of final enrolment
30/11/2011

Locations

Countries of recruitment
Japan

Study participating centre
First Department of Internal Medicine
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Sponsor information

Organisation
Niigata University Medical and Dental Hospital (Japan)

ROR
https://ror.org/03b0x6j22

Funder(s)

Funder type
Government

Funder Name
Niigata University Medical and Dental Hospital (Japan) - Fund for Clinical Studies

Funder Name
Trial also supported in part by:

Funder Name
Ministry of Education, Culture, Sports and Technology (Japan) - Grants for Scientific Studies entitled:

Funder Name

Basic study and clinical trial of angiogenesis by ex-vivo expanded erythroblasts (ref: 17590714, April 2005 - March 2007)

Funder Name
Ex-vivo expanded erythroblasts transplantation' for the treatment of patients with severe chronic lower limb ischemia (ref: 19590856, April 2007 - March 2009)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Abstract results		23/03/2018	12/04/2021	No	No