Effect of autologous Bone Marrow Derived Mesenchymal Stromal Cells prior to Lung Volume Reduction Surgery for Severe Pulmonary Emphysema
- a phase I safety and feasibility study -

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To test the safety and feasibility of intravenous administration of autologous BM-MSC after one-sided LVRS and prior to a second LVRS procedure for patients with end-stage pulmonary emphysema and to compare with historic lung function data of a...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Lower respiratory tract disorders (excl obstruction and infection)
Study type	Interventional

Summary

ID

NL-OMON33080

Source
ToetsingOnline

Brief title
Safety of autologous mesenchymal stemcells on severe pulmonary emphysema

Condition

- Lower respiratory tract disorders (excl obstruction and infection)

Synonym
smokers lungs, soft lungs

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: anti-inflammatory, emphysema, MSC's, tissue regeneration

Outcome measures

Primary outcome

Safety and feasibility of intravenous infusion of two doses of BM-MSC with 1 wk interval after the first LVRS and prior to a second LVRS. Safety will be evaluated according to WHO criteria and in addition change in outcome of lung function by the surgery and MSC treatment will be compared with a cohort of LUMC patients treated by lungvolumereduction surgery in LUMC and of whom similar lung function data were obtained.

Secondary outcome

Disease specific transpleural air leakage measured in days after the day of surgery.

The surgeon will insert a chest tube after removal of emphysematous tissue. Transpleural air leakage can be measured with a flow meter connected to drainage reservoir. The number of days with air leakage through the tube will be counted after each LVRS. The difference in days between the first and second LVRS session is the primary outcome parameter

Ex-vivo analysis of MSC-induced effects:

Immunohistochemical examination of resected tissue of both left (not MSC-treated) and right (MSC-treated) lung from each patient will be analysed

for inflammatory cell markers and markers of tissue repair and fibrosis.
Inflammatory cell infiltrates will be analyzed using markers for T cells (CD3, CD4 and CD8), B cells (CD20), macrophages (CD68), neutrophils (elastase), eosinophils (EG2), and mast cells (AA1; mast cell tryptase). To assess early fibrotic events, we will determine total collagen deposition and expression of mooth muscle actin, a smooth muscle cell marker that is also expressed in myofibroblasts. Ki67 staining will be used as a marker for proliferating cells, together with VEGF and other markers for tissue repair that will be further defined based on the findings. Finally, we will assess the local expression of hCAP18/LL-37, an antimicrobial peptide that has recently been identified as a chemoattractant for MSC. In this way we will compare MSC-induced effects within patients and between patients.
inn-vivo analysis of MSC on lung tissue:
Before LVRS and one year after the second LVRS, patients will be assessed for lung density by chest CT scan according to a published acquisition protocol. Both chest CT scans are part of the standard chain of procedures associated with 2-sided LVRS. The difference in 15th percentile point of the histogram of lung densities between left and right lung measured before and after surgery is a secondary end point.
Comparison of change in lung function due to treatment by current protocol compared with historic LVRC treatment from LUMC with MSC infusions.

Study description

Background summary

Emphysema is one of the two main components of chronic obstructive pulmonary disease (COPD) and contributes over many years to airway obstruction by the loss of elastic recoil around the smallest airways. Emphysema is induced by cigarette smoking and it is widely accepted that the disease is caused by excessive proteolytic activity by proteases and a chronic inflammatory process, characterized by a cellular influx consisting of macrophages, neutrophils and T cells. This inflammatory response is steroid resistant and leads to slow but persistent alveolar destruction, resulting in enlarged lungs with bullous parts in both lungs. In addition to a central role of innate immunity, recent studies suggest that also (auto)antigen specific immunity may play a role in the pathogenesis of COPD.
Currently, the only treatment available for severe emphysema is lung volume reduction surgery (LVRS) to remove the most destroyed parts of the lungs. The surgery is generally performed in two separate sessions with a 10-12 weeks interval, with each lung as a separate surgical target. This surgical treatment allows improved ventilation in the remaining less affected areas of the lungs as demonstrated by post-surgical clinical improvement of lung function and increased survival in a subgroup of patients. Delayed wound healing after LVRS is an important clinical problem. It may lead to prolonged hospital stay due to air leakage from the lungs into the thoracic cavity. Lung emphysema patients are at high risk for prolonged air leakage after this surgery, which is most likely explained by the inflammatory process related to the disease.
Mesenchymal stromal cells (MSC) are multipotent cells that can differentiate into several cell types, including fibroblasts, osteoblasts, adipocytes and chondrocyte progenitors. In recent years it has become evident that bone-marrow derived MSC (BM-MSC) have potent immunomodulatory effects on T and B cells in vitro and in animal models of chronic inflammation in vivo. In addition, it has been shown that MSC express or release a variety of soluble factors implicated in anti-apoptotic signaling and cell growth. Importantly, encouraging results have recently been obtained with the treatment of severe steroid resistant Graft versus Host Disease (GvHD) with donor (allogeneic) BM-MSC. Furthermore, in our institute autologous BM-MSC are currently under investigation for treatment of tissue injury due to autoimmune disease (Crohn*s Disease) and allogeneic immune responses (renal transplant recipients with biopsy proven subclinical rejection). The combination of the immunosuppressive, growth-potentiating and anti-apoptotic properties of BM-MSC may lead to accelerated wound healing after LVRS and might induce lung repair. In the present phase I study we will assess the safety and feasibility of intravenous (i.v.) administration of BM-MSC prior to LVRS in a small group of severe pulmonary emphysema patients. Results of this safety and feasibility study may lead to future studies on the use of BM-MSC for immunomodulation and induction of repair in patients with pulmonary emphysema and milder stages of COPD.

Study objective

To test the safety and feasibility of intravenous administration of autologous BM-MSC after one-sided LVRS and prior to a second LVRS procedure for patients with end-stage pulmonary emphysema and to compare with historic lung function data of a similar patient population from LUMC.

Study design

Open label, non-randomized, non-blinded, prospective clinical trial. Patients are operated in two sessions; initially on one lung without pre-surgical infusion of BM-MSC, followed by a second surgical procedure on the contralateral lung which is preceded by two i.v. infusions of BM-MSC one week apart at, 4 and 3 weeks prior to the lung surgery. The intervention consists of two doses of BM-MSC infusions of 1-2 x 10/6 MSC/kg body weight in 10 patients with a one week interval, 4 and 3 weeks prior to the second LVRS respectively.

Intervention

Two intravenous infusions of autologous bone marrow derived mesenchymal stemcells

Study burden and risks

Two CT scans, one as part of routine screening procedure prior to LVRS, one additional at the end of the 1 yr follow-up period; LVRS in 2 sessions as part of standard clinical care; BM aspiration (100 ml) during the first LVRS under general anesthesia; intravenous administration of two doses of BM-MSC prior to the second LVRS procedure; 10 visits to the hospital (8 routine), 2 extra for BM-MSC infusions.
Initial phase I studies involving autologous bone marrow-derived MSC showed that MSC could be successfully collected, culture-expanded ex-vivo for 4-7 weeks and administered to patients with hematological malignancies in complete remission. The transfusions contained up to 50 x 106 BM-MSC and were well tolerated without adverse reactions. In a subsequent phase I-II clinical trial in patients with breast cancer, autologous and expanded BM-MSC were co-infused with autologous peripheral blood progenitor cells. No toxicities were observed related to the transfusion of BM-MSC and hematopoietic reconstitution was rapid, suggesting some efficacy of BM-MSC transfusion on hematopoietic reconstitution.

In another multi-center phase I-II study, allogeneic donor BM-MSC were co-infused in patients with hematological malignancies undergoing matched sibling stem cell transplantation. Preliminary data suggests that there was no immediate toxicity following transfusion of BM-MSC and that there was a more rapid engraftment and a lower incidence of acute Graft versus Host Disease (GvHD) in comparison with historical controls.

The ability of BM-MSC to suppress immune responses following autologous bone marrow transplantation was initially shown in a case study of sever grade IV GvHD. Le Blanc et al. has reported that repeated administration of purified haploidentical human BM-MSC following allogeneic stem cell transplantation completely reversed GvHD. The results of this case study have recently been confirmed in a multicenter phase II trial for the treatment of severe acute GvHD, showing complete response in 30 of 55 patients treated with BM-MSC

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

For entry in the study, the following criteria must be met:
a) Men and women over 50 years of age and must have stopped smoking for more than 6 months.

b) Subject is willing to participate in the study and has signed the informed consent.
c) Subject must have emphysema in both lungs demonstrated on a chest CT scan.
d) Subjects must have less than 15% difference in lung density between left and right lung as assessed by PulmCMS software in chest CT scan DICOM files.
e) Subject must have FEV1 below 40% pred (post-bronchodilator).
f) Subject must have a Kco gastransfer factor < 40% pred.
g) Subject must have flat diaphragm as demonstrated on chest film.
h) Patients must be able to adhere to the study visit schedule and protocol requirements.
i) Patient must be willing to participate in a pre-operative rehabilitation protocol.
j) Patients must be able to give informed consent and the consent must be obtained prior to any study procedure.

Exclusion criteria

a) Patients with clinical and radiological evidence of bronchiectasis.
b) Patients suffering from renal- or hepatic failure.
c) A psychiatric, addictive, or any disorder that compromises ability to give truly informed consent for participation in this study.
d) Use of any investigational drug within 1 month prior to screening
e) Patients with pulmonary hypertension, with mean PAP above 30 mmHg assessed by ultrasound of the chest or by transoesophageal ultrasound.
f) Documented HIV infection.
g) Active hepatitis B, hepatitis C or TB.
h) Subjects who currently have or who have had an opportunistic infection (e.g., herpes zoster [shingles], cytomegalovirus, Pneumocystis carinii, aspergillosis, histoplasmosis, or mycobacteria other than TB) within 6 months prior to screening.
i) Current signs or symptoms of severe, progressive or uncontrolled renal, hepatic, hematologic, gastrointestinal, endocrine, cardiac, neurologic, or cerebral disease (including demyelinating diseases such as multiple sclerosis).
j) Malignancy within the past 5 years (except for squamous or basal cell carcinoma of the skin that has been treated with no evidence of recurrence).
k) History of lymphoproliferative disease including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy of unusual size or location (such as nodes in the posterior triangle of the neck, infra-clavicular, epitrochlear, or periaortic areas), or splenomegaly.
l) Known recent substance abuse (drug or alcohol).
m) Poor tolerability of venapuncture or lack of adequate venous access for required blood sampling during the study period.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-09-2010
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cells autologous

Ethics review

Approved WMO

Date:	27-10-2009
Application type:	First submission
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	EUCTR2009-013551-29-NL
CCMO	NL28562.000.09