ISRCTN18931678 https://doi.org/10.1186/ISRCTN18931678

Clinical trial for the treatment of pulmonary alveolar proteinosis by inhalation of recombinant human granulocyte-macrophage colony stimulating factor (GMCSF)

Submission date 08/04/2008	**Recruitment status** No longer recruiting	[_] Prospectively registered [_] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 04/06/2008	**Overall study status** Completed	
Last Edited 05/04/2012	**Condition category** Respiratory	

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

Contact name
Prof Koh Nakata

Contact details
Bioscience Medical Research Centre
Niigata University Medical and Dental Hospital
1-754 Asahimachi-dori
Chuo-ku
Niigata
Japan
951-8520

Additional identifiers

Protocol serial number
NH17-006

Study information

Scientific Title
Phase II clinical study of recombinant human granulocyte-macrophage colony stimulating factor (GMCSF) inhalation therapy for the treatment of patients with autoimmune (idiopathic) pulmonary alveolar proteinosis

Acronym
PAP GMCSF Inhalation Study

Study objectives
Autoimmune (idiopathic) pulmonary alveolar proteinosis (A-PAP) is characterized by excessive accumulation of surfactants in the alveoli and terminal bronchi that lead to the development of progressive dyspnea. The disease has been usually treated by whole-lung lavage under general anaesthesia or by repeated segmental lung lavage, which are stressful and painful for patients. In 1999 we discovered that the lungs and blood of patients with A-PAP contain large amounts of neutralizing autoantibody to granulocyte macrophage-colony stimulating factor (GM-CSF). Now it is thought that A-PAP is attributable to a reduction in the surfactant-degrading capability of alveolar macrophages as a result of the antibody. In recent years, Seymour et al. in Australia tried consecutive-day subcutaneous GM-CSF injection therapy, and reported that it improved the respiratory function of 44% of all severe cases of this disease without the need for pulmonary lavage. In 2001, we began using GM-CSF inhalation therapy to treat 3 cases of A-PAP (12 cycles of 7-day inhalation at intervals of 7 days, 250 μg/day) and found that it dramatically improved respiratory function and resulted in the disappearance of the autoantibody from alveolar lavage fluid. This study will be undertaken to evaluate the efficacy and safety of GM-CSF inhalation therapy in 30-40 patients with A-PAP.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Institutional Review Board (IRB) for the Clinical Trials of Pharmaceutical Agents and Medical Instruments, Niigata University Medical and Dental Hospital (ref: NH17-006)
Version 1: approved on 13/07/2005
Version 1.7: approved on 25/04/2007

Primary study design
Interventional

Study design
Phase II, open-label, non-randomised, single-arm, multi-centre trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Autoimmune (idiopathic) pulmonary alveolar proteinosis

Interventions
1. Untreated observation period: week 1-12
The investigator will arrange for the participant to visit the outpatient clinic immediately before, and 6 and 12 weeks after the start of the untreated observation period. During each visit the tests described below (resting arterial blood gas analysis, etc.) will be performed.

2. Induction treatment period: week 13-24
Patients will be treated with recombinant human yeast-derived GM-CSF (Leukine®; formerly Immunex Corporation and now Berlex, USA) administered with a LC-PLUS® jet nebuliser (PARI Respiratory Equipment, Inc.). Patients will be trained to self-administer inhalation therapy. Lyophilized 125 microgram of Leukine® will be dissolved in 2 ml of saline and inhaled by the nebulizer twice daily for 8 days and 6 days without inhalation during the 12 weeks.

3. Booster treatment period: week 25-36
During the following 12 weeks, the patients will be treated with 125 microgram of inhaled GM-CSF in 2 ml saline once daily for 4 days and no treatment for 10 days.

4. Monitoring during therapy
Patients will be administered with the initial doses and observed in a short admittance to a hospital. Outpatient follow-up will be every four weeks from week 4 until week 24 after initiation of therapy. The following will be carried out at the follow-ups:
a. Chest radiographs,
b. Resting arterial blood gas analyses,
c. Spirometry and diffusion capacity,
d. Complete blood count,
e. Tests of serum markers,
f. Computerised tomography (CT) scans
g. The Short Form-36 (SF-36) quality of life questionnaire

After the 6-month visit, the patients were assessed at 9, 12 and 18 months.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Granulocyte-macrophage colony stimulating factor (GMCSF)

Primary outcome(s)
1. Efficacy evaluation:
The primary end point will be an improvement in oxygenation as assessed by a >= 10 mm Hg decrease in the room air alveolar arterial oxygen gradient (A-aDO2). The therapy will be rated as effective in cases in which there is a >= 10 mmHg improvement in this parameter during the same period. The number of effective cases will be divided by the number of evaluation-capable cases among the total number of cases in the treatment group and that satisfy the inclusion criteria to obtain the response rate. The significance of the differences between A-aDO2 at the start and end of the untreated observation period and between the start and end of the induction treatment period will be tested by the paired t-test.

2. Safety evaluation:
During the therapy and follow-up visits, patients will be examined by a physician for signs of any drug-related toxicity, including the following points:
2.1. Progression of the respiratory failure, assessed every four weeks from week 4 until week 24 (6-month visit) after initiation of therapy, and then 9, 12 and 18 months
2.2. Allergic or anaphylactic reaction with the inhalation of GMCSF, assessed every four weeks

from week 4 until week 24 (6-month visit) after initiation of therapy, and then 9, 12 and 18 months
2.3. Abnormalities in laboratory findings including, but not limited to, leukocytosis, increased levels of serum creatinine and liver enzymes. These will be assessed at the start of the therapy and at outpatient follow-up at 12 and 24 weeks, and 9, 12 and 18 months
2.4. Common adverse effects caused by drug administration stated in National Cancer Institute Common Toxicity Criteria (NCI-CTC), assessed every four weeks from week 4 until week 24 (6-month visit) after initiation of therapy, and then 9, 12 and 18 months

Key secondary outcome(s)
1. The period during which the A-aDO2 level is maintained above the baseline A-aDO2 + 10 mmHg will be deemed the response period for patients in whom therapy is rated as effective. AaDO2 will be assessed before treatment and at outpatient follow-up every four weeks from week 4 until week 24, and then 9, 12 and 18 months
2. High-resolution computed tomography (HRCT) images before and after treatment will be compared. HRCT will be carried out before and at the end of the treatment (24 weeks after the start of treatment). The percentage of the area showing "ground-glass opacity" (including crazy paving) in the total area of a photocopied HRCT image is semi-quantified and rated on the six-grade scale. The mean grade will be calculated for each lung specimen.
3. The serum levels of the following respiratory function indicators will be measured before and after treatment: carcinoembryonic antigen (CEA), mucin-like antigen KL-6 (KL-6), surfactant protein A (SP-A), surfactant protein D (SP-D), and lactate dehydrogenase (LDH)
4. Bronchoalveolar lavage fluid will be checked before and at the end of the treatment (24 weeks after the start of treatment) for alveolar macrophage density, total cell count, and anti-GM-CSF autoantibody level
5. Six-minute gait test will be carried out before and at the end of the treatment (24 weeks after the start of treatment). Results will be analysed with regard to distance walked and reduction in oxygen saturation

Completion date
28/02/2009

Eligibility

Key inclusion criteria
1. Both males and females, age over 16 years and below 80 years (as of the date of registration)
2. Patients from whom informed consent has been obtained in writing
3. Patients who can be admitted to a hospital for a short period for evaluation at the start and the end of the treatment period
4. Patients with autoimmune (idiopathic) pulmonary alveolar proteinosis who satisfy either criterion A or B below and whose serum anti-GM-CSF autoantibody level is in the positive range (over 0.5 microgram/ml):
A: Typical pathological findings (pool of PAS-positive protein-like material in the alveoli) detected by transbronchial lung biopsy or surgical lung biopsy (thoracoscopic lung biopsy, etc.)
B: Typical findings in bronchoalveolar lavage fluid (turbid, protein-like material; decreased macrophage count)
5. Patients with resting PO2 below 75 mmHg at supine position

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Key exclusion criteria
1. White blood cell (WBC) of 12,000/microliter or more
2. Fever of 38 degrees centigrade or more
3. Grade 2 or severer oedema
4. Malignant disease of the bone marrow
5. Complication by congestive heart failure, angina pectoris, hemorrhagic tendency, primary lung carcinoma, metastatic lung carcinoma, bronchial asthma, etc., in which Leukine® therapy and its evaluation are considered as difficult
6. Treatment with other cytokines
7. Pregnant or possibly pregnant women, lactating women, and women who desire to become pregnant during the study period
8. Patients who have undergone whole-lung lavage or repeated segmental-lung lavage within 6 months before the start of the study (this criterion does not apply to patients for whom 6 months or more have elapsed after their last lavage)
9. Other patients judged to be inappropriate for the study by the attending physician (e.g., patients who are unlikely to complete treatment or are uncooperative)

Date of first enrolment
20/07/2005

Date of final enrolment
28/02/2009

Locations

Countries of recruitment
Japan

Study participating centre
Bioscience Medical Research Centre
Niigata
Japan
951-8520

Sponsor information

Organisation
Niigata University Medical and Dental Hospital (Japan)

ROR
https://ror.org/03b0x6j22

Funder(s)

Funder type
Government

Funder Name
Japanese Ministry of Education, Culture, Sports and Technology (Japan)

Funder Name
Japanese Ministry of Welfare and Labour (Japan)

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?
Results article	results	15/06/2010		Yes	No
Results article	results	01/02/2012		Yes	No