1. CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

a. Clinical Response: Patients may experience improvements in function and quality of life parameters. Reduction of inflammation in the alveoli has been seen in recent studies restoring airway functions. Subjects have also seen improvement in daily exercise capacity. Patients may also experience improvements in the St. George Respiratory Questionnaire.

2. PRELIMINARIES

a. Background: COPD is a lung disease that blocks airflow, causing patients to experience difficulty in breathing. COPD can also cause coughing, the production of mucus, and shortness of breath, wheezing, and constriction of the chest. COPD causes a restriction of airflow in and out of the body. COPD is a progressive disease that develops slowly, but consistently becomes worse over time. There are two main conditions characterized by patients with COPD: Chronic Bronchitis and Emphysema.

- **Chronic Bronchitis**: results in a thickening of the airways inner lining due to mucus formation, which leads to a decrease in lung capacity
- **Emphysema**: results in destruction of the air sacs walls and the walls between the air sacs, which leads to fewer air sacs and ultimately a reduction in gas exchange

b. Causes of COPD:

- **Lung Irritants**: extended exposure to lung irritants that impair the lungs
  - Firsthand smoke (cigarette, pipe, cigar, etc)
  - Air pollution, chemical fumes, or dust from environment
- **Alpha-1 Antitrypsin Deficiency**: A rare genetic condition where people have low levels of the protein made in the liver known as alpha-1 antitrypsin (AAT). This rare condition may make you more susceptible to lung irritants, causing COPD to progressive more aggressively.
- **Asthma**: is a chronic lung disease that inflames and narrows the breathing airways

C. Treatment Options:

- **Avoid Lung Irritants**
- **Make Lifestyle Changes**: These include: quitting smoking, maintain a healthy weight, meeting your nutritional needs, strengthening your muscles by increasing your physical activity, and any other initiative to improve your overall wellness.
- **Medicines**
  - Bronchodilators: Administered with a device called an inhaler, bronchodilators help relax the muscles around your airways. There are two types of bronchodilators: Short acting, which is used on an as needed basis with effects that last 4-6 hour periods, or long acting bronchodilators, which is used on a daily basis with effects that last 12 hours.
  - Combination Bronchodilators plus Inhaled Glucocorticosteroids (Steroids): Steroids are used in conjunction with bronchodilators to help reduce airway inflammation.
- **Vaccines**: COPD patients have higher risk for catching the flu and pneumonia. Vaccinations will help prevent serious health complications from occurring.
  - Flu Shots
  - Pneumococcal Vaccine
• **Pulmonary Rehabilitation**: is a program that helps improve the well-being of people who have COPD. Programs usually include initiatives to make lifestyle changes to help manage the COPD including exercise program, disease management training, and nutritional and psychological counseling.

• **Oxygen Therapy**: helps increase the level of oxygen in your blood by giving you oxygen through nasal prongs or a mask.

• **Surgery**
  > Bullectomy: the removal of over enlarged bullae(s) from the lungs
  > Lung Volume Reduction Surgery: the removal of damaged tissue from the lungs
  > Lung Transplant: removal of your damaged lung and replacement with a healthy lung from a deceased donor

### 3. POTENTIAL BENEFITS OF STEM CELL TREATMENT

Patients may experience improvements in function and quality of life parameters. Recent studies have shown that adipose stem cells reduce inflammation in the airway alveoli in response to cigarette smoke exposure or other airway irritants, and also decreased lung cell death¹. Stem cells have also the potential to stimulate the formation of new capillaries which may lead to tissue repair and oxygen delivery². Mesenchymal stem cells have shown the ability to potentially suppress autoreactive T-cells, inhibit macrophage activation and autoimmune response, improving lung functionality in COPD patients³. Improvement in lung capacity can be measured by exercise capacity. Patients’ improvements may be also monitored by the St. George Respiratory Questionnaire.


### 4. TREATMENT & DELIVERY METHOD REQUIRED

A. **Typical Recommended Treatment**: Adipose Derived Stem Cells

B. **Typical Delivery Method Required**: Autologous Ad-SVF containing adult stem cells are infused in 5-10 ml normal saline intravenously with a slow bolus push. Platelet rich plasma (PRP) can also be used in home nebulizer.

C. **Recommended dosing**: Recommended repeat dosing MSC’s every 6 to 8 weeks and based on patient’s symptoms. PRP in home nebulizer every 3 days.

### 5. POTENTIAL RISKS OF STEM CELL INJECTION(S)

There are possibilities for unwanted effects related to the local anesthesia, harvesting procedure, and injection of stem cells. Even with the most established protocol, adequate technique, and careful administration; a medical team may encounter uncontrollable events. Although there is no guarantee of any results, excellent results can be attained. The medical professional provides services in the most responsible, professional and diligent manner, always considering that surgeries imply risks. The risks of complications of adipose tissue harvesting and stem cell infusion are very low. Possible risks include but are not limited to:

- Pain at site of injections
- Bleeding at injection site
- Malaise
- Low-grade fever
- Hot flashes
- Itching at injection site
- Vascular spasm or obstruction
- Bruising
- Nerve or muscle injury
- Allergic reaction
- Unknown reaction up to and including death

### 6. FREQUENTLY ASKED QUESTIONS

1. How can stem cells help COPD?
   Stem cell therapy is a potential new alternative treatment to help manage the complications of COPD. Stem cells have the potential to replace and regenerate damaged cells in the body, including pulmonary cells. Mesenchymal stem cells, extracted from adipose tissue, help heal the body, replace any diseased cells and suppress pro-inflammatory cytokines protecting the lung tissue. This treatment is still being researched in order to fully understand the mechanism by which stem cells help improve COPD patients, however, the following improvements have been seen:
> Reduction of dyspnea
> Increased energy
> Increase in the ability to perform daily tasks without assistance
> Reduction of reliance on supplemental oxygen

2. How are stem cells administered for COPD treatment?
The adult stem cells are administered through an intravenous (IV) push.

3. How effective might stem cell therapy be?
Stem cell therapy studies for COPD are still in clinical trials. Each patient is different, and there is no guarantee of results or how effective it will be. However, results from clinical trials have shown improvement in COPD patients when subjected to the 6 minute walk test.

4. How long will it take to see any result?
There is no guarantee in the results or how soon they will be observed. In general, this process takes time and it is difficult to predict how long will it take to see some improvement. Some patients experience a benefit within a few weeks while others describe improvements beginning 3-6 months after treatment. According to studies, patients may continue to improve 12 months after treatment.

5. What should I bring with me on the treatment day?
You may bring an extra pair of clothes, including underwear. An abdominal compression binder/girdle is needed when the procedure is over. You may purchase the abdominal compression binder/girdle in our clinic or any pharmacy close to you. Also, a handful of dressings – abdominal pad (ABD) and paper tape. You will change to badge twice a day or more if needed for the first few days.

6. Are there any complications associated with this procedure?
Minimal bruising and soreness can be observed due to the liposuction procedure. This will normally last around 1-2 weeks, depending on the patient. Some patients have experienced headache or low grade fever. None of these symptoms were long lasting and resolved within 24-72 hours.

7. Does smoking or drinking affect the therapy?
Smoking and the consumption of alcohol has been shown to be harmful to stem cells. We advise that people do not smoke or drink during their treatment, and it must absolutely be avoided the week following the treatment.

8. Will anyone follow up with me after the procedure?
A team member will follow up with you 1 day, 1 week, 3 months, 6 months and 1 year after the procedure. Follow ups help us evaluate the effectiveness of our treatment, and improve treatment protocols. We will be monitoring your progress closely. We are happy to address any issues or questions at anytime.

**SUPPORTING ARTICLES**

Autologous Stromal Vascular Fraction in the Intravenous Treatment of End-Stage Chronic Obstructive Pulmonary Disease: A Phase I Trial of Safety and Tolerability.

**Comella K1, Blas JAP2, Ichim T2, Lopez J2, Limon J2, Moreno RC2.**

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**Abstract**
Chronic obstructive pulmonary disease (COPD) is a consistently progressive, ultimately fatal disease for which no treatment exists capable of either reversing or even interrupting its course. It afflicts more than 5% of the population in many countries, and it accordingly represents the third most frequent cause of death in the US, where it accounts for more than 600 billion in health care costs, morbidity, and mortality. Adipose tissue contains within its stromal compartment a high abundance of adipose stem/stromal cells (ASCs), which can be readily separated from the adipocyte population by methods which require less than 2 h of processing time and yield a concentrated cellular preparation termed the stromal vascular fraction (SVF). The SVF contains all cellular elements of fat, excluding adipocytes. Recent clinical studies have begun to explore the feasibility and safety of the local injection or intravascular delivery of SVF or more purified populations of ASCs derived by culture protocols. Several pre-clinical studies have demonstrated a remarkable ability of ASC to nearly fully ameliorate the progress of emphysema due to cigarette
smoke exposure as well as other causes. However, no prior clinical studies have evaluated the safety of administration of either ASC or SVF in subjects with COPD. We hypothesized that harvest, isolation, and immediate intravenous infusion of autologous SVF would be feasible and safe in subjects with COPD; and that such an approach, if ultimately determined to be efficacious as well as safe, would provide a highly practical method for treatment of COPD.

METHODS:
In this study, an initial phase I trial evaluating the early and delayed safety of SVF infusion was performed. Twelve subjects were enrolled in the study, in which adipose tissue was harvested using standard liposuction techniques, followed by SVF isolation and intravenous infusion of 150 - 300 million cells. Standardized questionnaires were administered to study feasibility as well as immediate and delayed outcomes and adverse events as primary endpoints. Secondary endpoints included subjective wellness and attitudes towards the procedure, as well as willingness to undergo the procedure a second time. The follow-up time ranged from 3 to 12 months, averaging 12 months.

RESULTS:
Of the 12 subjects, only one experienced an immediate adverse event, related to bruising from the liposuction. No observed pulmonary or cardiac issues were observed as related to the procedure. There were no deaths over the 12-month study period, and none identified in the subsequent telephonic follow-up. Attitudes toward the procedure were predominantly positive, and 92% of the study subjects expressed a desire to undergo the procedure a second time.

CONCLUSIONS:
This study is the first to demonstrate safety of SVF infusion in humans with serious pulmonary disease. Specifically, the use of intravenous infusion as a route to achieve pulmonary cellular targeting did not lead to clinical pulmonary compromise. The intravenous administration of SVF should be further explored as a potentially feasible and safe method for delivery leading to possible therapeutic benefit.

KEYWORDS:
Adipose stem/stromal cells; Adipose tissue; Cell therapy; Chronic obstructive pulmonary disease; Platelet rich plasma; Stem cells; Stromal vascular fraction
PMID: 28725319 PMCID: PMC5505307 DOI: 10.14740/jocmr3072w

2. A placebo-controlled, randomized trial of mesenchymal stem cells in COPD.
Authors: Weiss DJ, Casaburi R, Flannery R, LeRoux-Williams M, Tashkin DP. Source. Vermont Lung Center, University of Vermont College of Medicine, Burlington, VT 05405, USA. dweiss@uvm.edu

Abstract
BACKGROUND:
COPD is a devastating disease affecting millions worldwide. As disease pathogenesis includes both chronic pulmonary and systemic inflammation, antiinflammatory effects of systemically administered mesenchymal stem cells (MSCs) may decrease inflammation, resulting in improved lung function and quality of life. The goal of this study was to assess safety and to perform an initial evaluation of the potential efficacy of systemic MSC administration to patients with moderate to severe COPD.

METHODS:
Sixty-two patients at six sites were randomized to double-blinded IV infusions of either allogeneic MSCs (Prochymal; Osiris Therapeutics Inc) or vehicle control. Patients received four monthly infusions (100 × 10^6 cells/infusion) and were subsequently followed for 2 years after the first infusion. End points included comprehensive safety evaluation, pulmonary function testing (PFT), and quality-of-life indicators including questionnaires, 6MWT, and assessments of systemic inflammation.

RESULTS:
All study patients completed the full infusion protocol, and 74% completed the 2-year follow-up. There were no infusional toxicities and no deaths or serious adverse events deemed related to MSC administration. There were no significant differences in the overall number of adverse events, frequency of COPD exacerbations, or worsening of disease in patients treated with MSCs. There were no significant differences in PFTs or quality-of-life indicators; however, an early, significant decrease in levels of circulating C-reactive protein (CRP) was observed in patients treated with MSCs who had elevated CRP levels at study entry.

CONCLUSIONS:
Systemic MSC administration appears to be safe in patients with moderate to severe COPD and provides a basis for subsequent cell therapy investigations.

3. A protocol proposition of cell therapy for the treatment of Chronic Obstructive Pulmonary Disease.

Authors: Ribeiro-Paes JT, Stessuk T, Yonashiro Marcelino M, Arruda de Faria C, Quiqueto Marinelli T, de Oliveira Ribeiro-Paes MJ. Source Departamento de Ciências Biológicas, Universidade Estadual Paulista - Unesp - Assis, SP, Brasil. Electronic address: jtrpaes@yahoo.com.br.

Abstract
The main feature of pulmonary emphysema is airflow obstruction resulting from the destruction of the alveolar walls distal to the terminal bronchioles. Existing clinical approaches have improved and extended the quality of life of emphysema patients. However, no treatment currently exists that can change the disease course and cure the patient. The different therapeutic approaches that are available aim to increase survival and/or enhance the quality of life of emphysema patients. In this context, cell therapy is a promising therapeutic approach with great potential for degenerative pulmonary diseases. In this protocol proposition, all patients will be submitted to laboratory tests, such as evaluation of heart and lung function and routine examinations. Stem cells will be harvested by means of 10 punctures on each anterior iliac crest, collecting a total volume of 200mL bone marrow. After preparation, separation, counting and labeling (optional) of the mononuclear cells, the patients will receive an intravenous infusion from the pool of Bone Marrow Mononuclear Cells (BMMC). This article proposes a rational and safe clinical cellular therapy protocol which has the potential for developing new projects and can serve as a methodological reference for formulating clinical application protocols related to the use of cellular therapy in COPD. This study protocol was submitted and approved by the Brazilian National Committee of Ethics in Research (CONEP - Brazil) registration number 14764. It is also registered in ClinicalTrials.gov (NCT01110252).


4. Phase I clinical trial of cell therapy in patients with advanced chronic obstructive pulmonary disease: follow-up of up to 3 years.

Authors: Stessuk T, Ruiz MA, Greco OT, Bilaqui A, Ribeiro-Paes MJ, Ribeiro-Paes JT. Source Universidade de São Paulo - USP, São Paulo, SP, Brazil.

Abstract
BACKGROUND:
Chronic obstructive pulmonary disease is a major inflammatory disease of the airways and an enormous therapeutic challenge. Within the spectrum of chronic obstructive pulmonary disease, pulmonary emphysema is characterized by the destruction of the alveolar walls with an increase in the air spaces distal to the terminal bronchioles but without significant pulmonary fibrosis. Therapeutic options are limited and palliative since they are unable to promote morphological and functional regeneration of the alveolar tissue. In this context, new therapeutic approaches, such as cell therapy with adult stem cells, are being evaluated.

OBJECTIVE:
This article aims to describe the follow-up of up to 3 years after the beginning of a phase I clinical trial and discuss the spirometry parameters achieved by patients with advanced pulmonary emphysema treated with bone marrow mononuclear cells.

METHODS:
Four patients with advanced pulmonary emphysema were submitted to autologous infusion of bone marrow mononuclear cells. Follow-ups were performed by spirometry up to 3 years after the procedure.

RESULTS:
The results showed that autologous cell therapy in patients having chronic obstructive pulmonary disease is a safe procedure and free of adverse effects. There was an improvement in laboratory parameters (spirometry) and a slowing down in the process of pathological degeneration. Also, patients reported improvements in the clinical condition and quality of life.

CONCLUSIONS:
Despite being in the initial stage and in spite of the small sample, the results of the clinical protocol of cell therapy in advanced pulmonary emphysema as proposed in this study, open new therapeutic perspectives in chronic obstructive pulmonary disease. It is worth emphasizing that this study corresponds to the first study in the literature that reports a change in the natural history of pulmonary emphysema after the use of cell therapy with a pool of bone marrow mononuclear cells.

5. Mesenchymal stem cell therapy in lung disorders: pathogenesis of lung diseases and mechanism of action of mesenchymal stem cell.

Authors: Inamdar AC, Inamdar AA. Source 1Saiseva Biotech Pvt. Ltd., Satara, India.

Abstract

Lung disorders such as asthma, acute respiratory distress syndrome (ARDS), chronic obstructive lung disease (COPD), and interstitial lung disease (ILD) show a few common threads of pathogenic mechanisms: inflammation, aberrant immune activity, infection, and fibrosis. Currently no modes of effective treatment are available for ILD or emphysema. Being anti-inflammatory, immunomodulatory, and regenerative in nature, the administration of mesenchymal stem cells (MSCs) has shown the capacity to control immune dysfunction and inflammation in the lung. The intravenous infusion of MSCs, the common mode of delivery, is followed by their enraptement in lung vasculature before MSCs reach to other organ systems thus indicating the feasible and promising approach of MSCs therapy for lung diseases. In this review, we discuss the mechanistic basis for MSCs therapy for asthma, ARDS, COPD, and ILD.


6. Mesenchymal stem cell therapy for the treatment of chronic obstructive pulmonary disease

Authors: Bruno D’Agostino, Nikol Sullo, Dario Siniscalco, Antonella De Angelis, Francesco Rossi

Abstract

Recent studies have revealed that adult stem cells such as bone marrow-derived cells contribute to lung tissue regeneration and protection, and thus administration of exogenous stem/progenitor cells may be a potent next-generation therapy for COPD. Pathogenesis of COPD is characterized by an upregulation of inflammatory processes leading to irreversible events such as apoptosis of epithelial cells, proteolysis of the terminal air-space and lung extracellular matrix components. The available pharmacological treatments are essentially symptomatic, therefore, there is a need to develop more effective therapeutic strategies. It has been previously demonstrated that transplanted MSC home to the lung in response to lung injury and adopt phenotypes of alveolar epithelial cells, endothelial cells, fibroblasts and bronchial epithelial cells. However, engraftment and differentiation are now felt to be rare occurrences and other mechanisms might be involved and play a more important role. Importantly, MSCs protect lung tissue through suppression of proinflammatory cytokines, and through triggering production of reparative growth factors.

Accordingly, it is not clear if and how these cells will be able to repair, to slow or to prevent the disease. This article reviews recent advances in regenerative medicine in COPD and highlights that their potential application although promising and very attractive, are still a far away opinion.

Expert Opinion on Biological Therapy, May 2010, Vol. 10, No. 5 : Pages 681-68


Authors: Weiss DJ. Source. Department of Medicine, University of Vermont College of Medicine, Burlington, VT, 05405.

Abstract

Lung diseases remain a significant and devastating cause of morbidity and mortality worldwide. In contrast to many other major diseases, lung diseases notably chronic obstructive pulmonary diseases (COPD), including both asthma and emphysema, are increasing in prevalence and COPD is expected to become the 3rd leading cause of disease mortality worldwide by 2020. New therapeutic options are desperately needed. A rapidly growing number of investigations of stem cells and cell therapies in lung biology and diseases as well as in ex vivo lung bioengineering have offered exciting new avenues for advancing knowledge of lung biology as well as providing novel potential therapeutic approaches for lung diseases. These initial observations have led to a growing exploration of endothelial progenitor cells and mesenchymal stem (stromal) cells in clinical trials of pulmonary hypertension and chronic obstructive pulmonary disease (COPD) with other clinical investigations planned. Ex vivo bioengineering of the trachea, larynx, diaphragm, and the lung itself with both biosynthetic constructs as well as decellularized tissues have been utilized to explore engineering both airway and vascular systems of the lung. Lung is thus a ripe organ for a variety of cell therapy and regenerative medicine approaches. Current state-of-the-art progress for each of the above areas will be presented as will discussion of current considerations for cell therapy based clinical trials in lung diseases. Stem Cells 2013. Stem Cells. 2013 Aug 20. doi: 10.1002/stem.1506. [Epub ahead of print]

8. Adult stem cells for chronic lung diseases.

Authors: Mora AL, Rojas M. Source Division of Pulmonary, Allergy and Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA.; Vascular Medicine Institute, University of Pittsburgh School of Medicine, Pittsburgh, PA.
Abstract
Idiopathic pulmonary fibrosis (IPF) and Chronic Obstructive Pulmonary Disease (COPD) are chronic, progressive and lethal lung diseases. The incidence of IPF and COPD increases with age, independent of exposure to common environmental risk factors. At present, there is limited understanding of the relationship between aging and the development of chronic lung diseases. One hypothesis is that chronic injury drives to exhaustion the local and systemic repair responses in the lung. These changes are accentuated during aging where there is a progressive accumulation of senescent cells. Recently, stem cells have emerged as a critical reparative mechanism for lung injury. In this review, we discuss the repair response of bone marrow derived mesenchymal stem cells (B-MSCs) after lung injury and how their function is affected by aging. Our own work has demonstrated a protective role of B-MSCs in several animal models of acute and chronic lung injury. We recently demonstrated the association, using animal models, between age and an increase in the susceptibility to develop severe injury and fibrosis. At the same time, we have identified functional differences between B-MSCs isolated from young and old animals. Further studies are required to understand the functional impairment of aging B-MSCs, ultimately leading to a rapid stem cell depletion or fatigue, interfering with their ability to play a protective role in lung injury. The elucidation of these events will help in the development of rational and new therapeutic strategies for COPD and IPF.

9. Experimental basis and new insights for cell therapy in COPD
Authors: de Faria CA, de las Heras Kozma R, Stessuk T, Ribeiro-Paes JT.

Source
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Abstract
Chronic Obstructive Pulmonary Disease (COPD) can be briefly described as air flow limitation and chronic dyspnea associated to an inflammatory response of the respiratory tract to noxious particles and gasses. Its main feature is the obstruction of airflow and consequent chronic dyspnea. Despite recent advances, and the development of new therapeutic, medical and clinical approaches, a curative therapy is yet to be achieved. Therapies involving the use of tissue-specific or donor derived cells present a promising alternative in the treatment of degenerative diseases and injuries. Recent studies demonstrate that mesenchymal stem cells have the capacity to modulate immune responses in acute lung injury and pulmonary fibrosis in animal models, as well as in human patients. Due to these aspects, different groups raised the possibility that the stem cells from different sources, such as those found in bone marrow or adipose tissue, could act preventing the emphysematous lesion progression. In this paper, it is proposed a review of the current state of the art and future perspectives on the use of cell therapy in obstructive lung diseases.
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