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TREATMENT OF A CHRONIC OBSTRUCTIVE PULMONARY DISEASE CASE WITH REGENTIME® PROCEDURE

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ABSTRACT

Chronic Obstructive Pulmonary Disease (COPD) is a common disease associated with high morbidity and mortality rates. It is characterized by airway and parenchymal inflammation leading to airway narrowing, decreased lung recoil, and eventual airflow limitation. Despite the advance in therapeutic approaches, no curative clinical treatment for COPD exists. We present the case of a 74-year-old gentleman diagnosed with COPD who underwent stem cell therapy with the Regentime® Procedure. This technique uses Autologous Bone Marrow -Mononuclear Stem Cells (BM-MSCs) which are partially differentiated and specifically redirected to the desired organ. Clinical follow-up 5 years after transplantation showed a decrease in major symptoms, including dyspnea, cough, fatigue, and decreased oxygen requirement. However, regression was registered during the past 2 years during which the patient's oxygen requirement increased for optimal oxygen saturation. The results obtained support stem cell-based therapy as a promising therapeutic option for patients suffering from COPD.

KEYWORDS: *Regentime® Procedure, Bone Marrow-Mesenchymal Stem Cells, Chronic Obstructive Pulmonary Disease.*

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is the third most common cause of morbidity and mortality worldwide, characterized by persistent airflow limitation and tissue destruction [**Error! Reference source not found.**]. It is caused by prolonged exposure to harmful particles, notably cigarette smoke, leading to chronic inflammation and structural lung changes [2].

The pathophysiology of COPD involves oxidative stress and protease/antiprotease imbalance affecting the airways, lung parenchyma, and pulmonary vasculature [3].
The release of multiple inflammatory mediators, oxidants, and excess proteases leads to alveolar sacs destruction with a subsequent loss of elastic recoil and obstructive physiology

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[4]. COPD patients typically present with progressive dyspnea, cough, and sputum production [1]. The 4-year survival rate of COPD patients can be predicted using a unique scoring system, the BODE index. It is based on FEV1 (forced expiratory volume in the first second), 6-minute walking distance, mMRC (modified medical research council) dyspnea scale, and body mass index. The estimated 4-year survival ranges from 18 to 80% depending on the patient's BODE score (the higher the index, the worse the condition) [1, 5]. Due to the absence of a curative therapeutic option that prevents disease progression, the treatment of COPD using mononuclear stem cells has been suggested. MSCs have progenitor and immune-regulatory properties that implicated them in the potential clinical application in treating immune-based diseases such as COPD [6].

We report the case of a 74-year-old patient diagnosed with group D COPD for more than 13 years who underwent stem cell therapy with the Regentime® procedure. This technique uses partially differentiated and specifically redirected Autologous Bone Marrow Mononuclear Stem Cells (BM-MSCs) (trademark ID number: 168469). A 7-year clinical follow-up after stem cell therapy for the patient in our case revealed a decrease in major symptoms and oxygen requirement, notably during the first 5 years following therapy.

Case Presentation

A 67-year-old man presented as an outpatient in 2015 for a trial of stem cell therapy for COPD. The patient was diagnosed with group D COPD in 2009 (mMRC score of 4, COPD assessment test score of 26, and multiple moderate exacerbations): he claimed that he stopped for breath after a few minutes of walking, had a chronic cough that was occasionally productive, often felt chest tightness, felt breathless after trying to walk up a hill, was limiting doing activities at home, was not so confident leaving his house knowing his lung condition, did not always sleep soundly, and has limited energy. He had a smoking history of 110 pack-year at presentation and no other comorbidities. The patient stated that at the time of diagnosis (in 2009), his spirometry testing revealed an obstructive pattern confirming COPD diagnosis, chest imaging showed hyperinflation and flattening of the diaphragm, and arterial blood gas indicated the need for long-term oxygen therapy. He had a BODE index score of 9/10 with an estimated 4-year survival rate of 18% [1], and a calculated estimated 12-year survival rate of 0.58% (0.18*0.18*0.18*100). At his presentation in 2015, he was on oxygen therapy by nasal cannula alternating with bi-level positive airway pressure (BiPAP), long-acting beta-agonists, long-acting anticholinergics, and inhaled corticosteroids as a chronic treatment.

The patient chose to try stem-cell therapy after traditional treatments failed to improve his quality of life over years. He underwent the Regentime® Procedure which consists of five steps:

a. Pre-lab stage

The patient was injected twice with 600 mcg of Filgrastim (Granulocyte Colony Stimulating Factor) intramuscularly in a window of 12 hours. A few hours after the last dose, an increase in the white blood cell count was documented.

b. The Bone Marrow Collection stage

Using aspiration syringes filled with 50,000 units of 10% heparin sodium, bone marrow aspiration was done bilaterally under local anesthesia: 100 mL were collected from each posterior superior iliac crest. The aspirate was transferred into a transfusion bag under sterile conditions (closed system technique). The bag was held at 22ºC on a slow three-dimensional laboratory shaker.

c. Laboratory stage

The bone marrow extract was centrifuged at 1830 RCF for 20 minutes. The cellular buffy coat including BM-MSCs was then collected. The BM-MSCs were incubated with sheep lungs ultra-filtrate (ACE|PICO PULMO) at 22°C on a shaker for 24 hours.

d. Transplantation stage

Following the 24-hour incubation period, the patient started receiving progenitor stem cells via 15-minute aerosol inhalation repetitively every 3 hours for a total of 6 sessions. Each session was administered in parallel with intravenous installation of 10 million stem cells (1 mL) in 100 mL of normal saline solution.

e. Post-transplantation stage

The patient was monitored in his hospital room for 2 days for continuous vital signs evaluation and recording of any undesirable effect.

RESULTS

Following his hospital discharge, the patient was monitored at home for 4 weeks. He resumed the same medications he was on before stem cell therapy. The patient was followed-up every 6 months for 7 years for clinical assessment. He claimed that he experienced no undesirable effects following stem cell therapy and reported that during the first 5 years following stem cell therapy, his symptoms improved progressively, including a decrease in dyspnea, cough, and fatigue. Moreover, he claimed that his need for oxygen support decreased; our following team registered that his oxygen saturation in room air did not drop below 89%. However, during the 6^{th} and 7^{th} years post-transplant, he started reusing an oxygen concentrator as his O2 saturation restarted to drop occasionally below 89% on room air. BiPAP was initiated again during sleep.

DISCUSSION

Key results and comparison with the literature

COPD is a leading cause of death globally due to its limited therapeutic options, characterized by a progressive and debilitating course of disease that affects over 390 million people worldwide [7]. It is caused by prolonged exposure to harmful particles and is marked by airway inflammation leading to long-term progressive respiratory symptoms and an obstructive lung disease pattern affecting the patients' quality

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of life [8]. Our patient underwent stem cell therapy by inhalation and intravenous infusion 6 years after diagnosis with group D COPD. Clinical follow-up more than 7 years following stem cell therapy revealed a decreased need for oxygen support and a progressive improvement in symptoms including dyspnea, cough, and fatigue, notably during the first 5 years following transplantation. Despite the calculated estimated 0.58% 12-year survival rate of our patient, he is still surviving after more than 13 years of his COPD diagnosis date, with reported progressively improved quality of life.

Our results suggesting decreased mortality and improved quality of life are supported by Squassoni, SD. et al. (2021) who found that the infusion of autologous bone marrow mononuclear cells in patients suffering from moderate to severe COPD improved alveolar gas exchange and diffusion capacity after 12 months [9]. Similar results were reported by Ribeiro-Paes, JT. et al. (2011) who applied stem cell therapy through intravenous infusion to patients with advanced COPD. They claimed an improvement in their clinical condition, a greater time tolerance off oxygen, and a greater tolerance to effort without a significant drop in oxygen saturation [10]. Further, in their study consisting of intravenous BM-MSCs administration to patients with severe emphysema, Stolk, J. et al. (2016) found no undesirable effects and a three-fold increased endothelial marker expression in emphysematous lung tissue suggesting microvascular responsiveness of severely affected lung areas 12 months following therapy [11]. Therefore, stem cell therapy for COPD showed promising results regarding survival, long-term safety, and improvement of patients' quality of life as an adjunctive to COPD traditional drugs.

Possible mechanisms by which stem cell therapy might decrease COPD progression

The mechanisms by which stem cells can potentially decrease COPD progression have been examined in the literature. First, alveolar epithelial cell apoptosis plays an important role in COPD pathogenesis and is mainly due to blocking the vascular endothelial growth factor (VEGF) signaling pathway. MSCs present an anti-apoptotic effect on the alveolar epithelium through the up-regulation of VEGF [12, 13] and have the potential to differentiate into alveolar epithelium [14], which can help restore lung tissue structure.

Second, exposure to noxious particles such as cigarette smoke is known to be associated with inflammatory and oxidative processes favoring the protease/antiprotease imbalance. This leads to extracellular matrix degradation through metalloproteinases (MMP-9 and MMP-12), promoting alveolar wall destruction and airspace enlargement [12]. The administration of MSCs into the lungs is suggested to reverse the induction of matrix metalloproteinases, restoring the protease/antiprotease balance [13].

Third, the administration of pulmonary MSCs may interfere with the inflammatory process involved in COPD pathogenesis. MSCs are thought to down-regulate pro-inflammatory mediators such as tumor necrosis factor-α, interleukin 1-ß, and interleukin 6 [13]. MSCs are further suggested to decrease oxidative stress by increasing heme oxygenase-1 levels, which presents anti-oxidative and cytoprotective effects [12, 15].

Subsequently, treatment of COPD patients with MSCs administration presents promising effects involving the differentiation of MSCs into alveolar epithelium, the restoration of protease/anti-protease balance, the modulation of inflammatory processes, and the decrease in oxidative stress.

Limitations and strengths

Some of the limitations of this case report should be acknowledged such as the lack of documented data; follow-up on the case was only clinical. Second, our results suggest that improved quality of life needs to be further validated by large-scale prospective studies, and long-term safety should be studied. Third, appropriate dosing, routes, and infusion rates need to be assessed to optimize treatment.

Meanwhile, the strengths of this report are also noteworthy since it is the first global case report of COPD treatment with stem cell transplantation through both inhalation and intravenously, which might have increased the patient's chances of improvement.

CONCLUSION

COPD is among the leading causes of death worldwide. The currently available therapies failed to prevent disease progression and decrease mortality. Therefore, the need for a potentially curative treatment emerged as a trial to decrease death rates. The Regentime® Procedure is based on the transplantation of proliferated partially differentiated and specifically redirected autologous adult bone marrow-derived mononuclear progenitor stem cells to targeted populations. The application of this procedure to our patients showed promising results regarding decreased mortality and a better quality of life. This suggested the Regentime® Procedure to be a potential key therapy in improving the lung function of COPD patients. However, larger-scale clinical trials are essential to optimize treatment doses and routes.

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