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

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Abstract

Background: 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: Stromal vascular fraction; Platelet rich plasma; Adipose stem/stromal cells; Stem cells; Adipose tissue; Chronic obstructive pulmonary disease; Cell therapy

Introduction

Chronic obstructive pulmonary disease (COPD), an umbrella term covering chronic bronchitis and emphysema, is the fourth leading cause of death in the United States and is projected to be the third by 2020 [1]. COPD is associated with an exaggerated chronic inflammatory response responsible for airway abnormalities including bronchiolitis constriction and parenchymal architectural distortion. Subjects generally undergo a progression of declining lung function, characterized by intensification of cough, shortness of breath, and increased sputum production [2]. Extra-pulmonary manifestations of COPD include osteoporosis, cardiovascular disease, skeletal muscle abnormalities, and depression. There is currently no cure, and the manifestations can only be treated symptomatically [3]. Ultimately these symptoms progress from a loss of quality of life...
life to a loss of life.

Cellular therapy with mesenchymal stem cells has been identified as having the potential to ameliorate diseases like COPD. Bone marrow mesenchymal stem cells (BM-MSCs) are a population of adherent, non-hematopoietic cells expressing markers such as CD90, CD105, and CD73, while lacking expression of CD14, CD34, and CD45. They have been shown in multiple models to be active in modulating inflammation, both by direct cellular interactions as well as by paracrine signaling [4]. These cells are actively being explored in clinical trials evaluating their immune- and inflammatory-modulating capabilities. They appear to have great promise but also suffer from shortcomings, including the need for significant culture expansion, which may be attended by alterations in gene expression [5]. Cultured BM-MSCs have recently been evaluated in a limited clinical trial addressing COPD, and while their infusion was associated with reduction in systemic inflammation as noted by C-reactive protein (CRP) levels, their administration has not yet been shown to be efficacious in altering the pulmonary manifestation of COPD [6].

More recently, adipose tissue-derived mesenchymal stem cells (ASCs or AD-MSCs) have been explored with respect to their activity in diseases involving significant inflammatory or degenerative components. Intravenous infusion of cultured ASC has been demonstrated to remarkably ameliorate the onset and progression of smoke exposure-induced emphysema in a rodent model [7]. These cells are significantly more abundant in lipo-aspirated fat tissue than are BM-MSC within aspirated bone marrow. Tens to hundreds of millions of ASC can be obtained in the context of the stromal vascular fraction (SVF) obtained from 20 - 200 mL of adipose tissue under local anesthesia, with minimal morbidity and without requiring culture expansion. This sets the stage for their practical use at the point-of-care, in which a preparation of ASC can be provided for infusion or injection within 1 - 2 h after lipo-aspiration.

Several studies to date have shown the feasibility of intravenous infusion of cultured MSC or ASC; and pre-clinical studies have clearly demonstrated significant trapping of these cells within the pulmonary circulation [8]. Cells administered in this manner are culture-expanded and therefore have a minimal amount of matrix and complement components associated with them. Since SVF extraction does not remove non-cellular components to the degree accomplished through culture expansion, safety studies must be conducted to evaluate the outcome of intravenous SVF infusion. The use of SVF has been reported in a variety of indications including osteoarthritis [9], degenerative disc disease [10], sclerosis [11], congestive heart failure [12], multiple sclerosis [13] and tendinopathy [14]. Intravenous infusion of SVF has indeed been demonstrated to be safe in some small studies [13], yet no study to date has evaluated the safety of non-culture expanded SVF in a patient series, particularly in subjects with COPD. In this study, a non-randomized, open label trial of immediate, intravenous autologous SVF re-infusion is performed. The primary endpoints are immediate and long-term safety, with a follow-up interval of 12 months. Study participants were also queried as to their willingness to undergo the procedure again and their perception of infusion utility in maintaining their health and slowing the progress of their disease.

Materials and Methods

The clinical trial design was reviewed and approved for conduct at the Angeles Hospital in Tijuana, Mexico, by the Institutional Review Board. It was then submitted for review and listed on the database www.clinicaltrials.gov as per international requirements.

Inclusion/exclusion criteria

Subjects were enrolled in this study according to their concordance with strict inclusion and exclusion criteria. Inclusion criteria were the following: 1) ages 40 - 80 years old; 2) a prior radiographic diagnosis of COPD under maximal medical management; 3) COPD Global Initiative for Chronic Obstructive Lung Disease (GOLD) score of III or IV indicating at least a FEV1/FVC < 0.70 and FEV1 49% or less of normal; 4) able to sign informed consent for the procedure; and 5) able to travel to the treatment center and undergo the procedure.

Exclusion criteria were the following: 1) age less than 40 or greater than 80; 2) pregnancy and/or unwillingness to maintain non-pregnant status during the study period; 3) presence of active infectious diseases including HIV, HTLV, HBV, HCV, or CMV; 4) presence of active malignancy; 5) evidence of heart, kidney, or liver failure as determined by abnormal laboratory values; 6) utilization of anti-coagulants for any indication; and 7) active or uncontrolled psychiatric illness.

Preoperative evaluation

Subjects were thoroughly screened before the procedure for evidence of infirmity that could specifically increase the medical risk of liposuction and re-infusion. A history and physical was performed, and electrocardiogram, chest radiograph, and full laboratory studies were obtained to evaluate pre-procedural heart, liver, kidney, and metabolic parameters.

Method of harvest and infusion

After evaluation and informed consent, subjects were taken to the operating room for liposuction by a board certified plastic surgeon. Under sterile conditions, tumescent solution (1-L saline with 50 mL of 1% lidocaine and 1 mg of epinephrine) was infiltrated into the abdomen or thighs. After appropriate time for anesthetic and hemostatic effect, 120 mL of fat was removed. Fat was then transferred to the sterile processing facility and digested with enzyme (Adipolase™ Enzyme, US Stem Cell Inc., Sunrise, FL) for 45 min to release the SVF. After processing and purification involving centrifugation and repetitive wash steps, the SVF was resuspended into 1 L of 0.9% NaCl saline. This autologous SVF was infused over 2 h intravenously via the antecubital vein. During this time, subjects were continuously monitored via pulse oximetry and
Electrocardiography for any evidence of cardiac or pulmonary instability.

Post-procedure monitoring

After the procedure, subjects were returned to the hospital ward for overnight monitoring. Discharge criteria were met when examination of the study participants confirmed that they were in a pre-procedural state of overall health. Follow-up was performed by designees within the treatment team via phone interviews once a week for the first month, and then once a month for the next 11 months. Independent phone interviews were performed subsequently during a several week time period, by two interviewers entirely uninvolved in initial recruitment, therapy, or the follow-up interviews conducted by the treatment team.

St. George Respiratory Questionnaire (SGRQ) was collected for some of the study participants. The SGRQ is an index developed to identify the quality of life of patients by measuring and quantifying health-related health status of patients with airflow obstruction. Forms were completed by patients at the time of treatment and at 3 and 6 months after procedure. Post-procedure forms were submitted by email by the subjects.

Results

Pre-intervention patient demographics

Subjects ranged between the ages of 57 and 75, with an average of 69 years of age. The ratio of male to female study participants was 1:1. All subjects had end-stage COPD and 25% were on a lung transplant list in their home state. All but one subject learned of this trial via the internet; one subject learned of its existence via another subject who had participated previously. Smoking was the main environmental contributor to COPD in this population, with 20 - 100 pack-year histories of total smoking represented. None of the subjects admitted to continued or current tobacco use. Almost all subjects were on therapeutic oxygen (2 L/min most commonly) at all times, and 75% had experienced at least one hospital admission for respiratory decompensation within the last 12 months. Most subjects had consulted with their primary care and specialty physicians prior to enrolling in the trial. In general, primary care physicians were indifferent or supportive, while pulmonologists were indifferent or negative in their opinion about the decision to participate in the trial.

Harvest/infusion/immediate post-operative safety

During the liposuction procedure, 120 mL of adipose tissue were removed. Nucleated cells were enumerated by manual count, and these counts revealed an average of 187 million cells for infusion, with a range from 132 to 237 million total cells, for a yield of 0.9 - 1.9 million nucleated cells/mL.

As is seen in Table 1, two subjects suffered pain during the procedure, and one had an infiltration injury of the hand. The remaining subjects described a comfortable and uneventful extraction and infusion procedure.

Study participants were closely observed during and immediately following the cell infusion to verify the safety of the procedure, with special attention to the cardiac and pulmonary systems. No adverse events, including instances of anaphylaxis, electrocardiogram abnormalities, rhythm disturbances (including bradycardia or tachycardia), oxygen desaturation, fever (temperature > 38.6 °C), or subjective feelings of discomfort, were noted in conjunction with the infusion.

Long-term safety

Close contact with subjects during the period of study allowed for measurement of attitudes and perceptions of the treatment on the disease process. Table 2 relates the post-infusion demographics and attitudes. At the time of data assembly, subjects had been followed on average for 18 months, with a range of 12 - 28 months having elapsed prior to the interview conducted by the research team independent from the treatment team. When queried about the subjective effect and time course of any noted effects, three stated that there was no effect of the treatment, four noted a subjective sense of benefit within a day, and five noted a gradual improvement, with maximal improvement noted at approximately 1 month following infusion. Three of the responders described a loss of the initial perceived benefit occurring between 1 and 3 months. The remaining six of these nine subjects still confirmed a beneficial effect on their perceived quality of life at 12 - 18 months. All subjects except one indicated that they would be willing to participate in the study and undergo the procedures again.

Several of the participants noted a decrease in their frequency of oxygen utilization at 12 months. Of the subjects who described positive effects from the SVF infusions, these often included a subjective overall feeling of wellness. Many subjects described a general improvement in their subjective activity level and appearance, with several commenting on a reduction in actinic keratoses, decreased pallor, and increased energy or stamina.

SGRQ showed statistically significant improvements at both 3 and 6 months after treatment. SGRQ at baseline (n = 12) was 73. The subjects quality of life score improved to 45 at 3 months after treatment (n = 10, P = 0.005) and 44 at 6 months after treatment (n = 7, P = 0.008).

Discussion

In this study, a phase I clinical study of autologous SVF infusion in subjects with COPD was conducted with a non-randomized open label treatment design, with a goal of obtaining early data concerning the primary endpoints of feasibility and safety, as well as to obtain any early evidence of efficacy. The evaluation of safety was based on a compilation of observations made at the time of SVF infusion, as well as telephonic
### Table 1. Study Participant Demographics

| Age | Sex | Method of search | Local physician input on study participation | Smoking (PYH) | Infusion side effects | Pre ASC oxygen | Hospitalizations pre ASC |
|-----|-----|------------------|---------------------------------------------|---------------|-----------------------|----------------|-------------------------|
| 72  | M   | Internet         | Pulmonologist: indifferent                   | 40            | None                  | 3              | 1 hospital, ER 6 - 8 wks prior |
| M   |     |                  | Pulmonologist: supportive                   | 100           | None                  | 3              | 1                       |
| F   |     | Internet         | Physicians indifferent                       | 75            | None                  | 2              | Monthly                 |
| F   |     | Internet         | Internist: supportive; pulmonologist: recommended against | 70            | None                  | 2              | Bi-yearly               |
| 70  | M   | Internet         | Pulmonologist: indifferent                   | 50            | Liposuction painful, IV infiltration: new IV started | 0              | 1 ER                    |
| 61  | F   | Internet         | Internist: supportive; pulmonologist/ cardiologist against | 40            | None                  | 2              | No                      |
| 73  | F   | Internet         | Pulmonologist: recommended against           | 45            | None                  | 2              | No                      |
| F   |     | Internet         | Physician indifferent                        | 50            | None                  | 2              | 1 ER                    |
| 69  | M   | Internet         | Did not consult with physician               | 60            | None                  | 2              | 1 ER                    |
| 57  | F   | Internet         | Kaiser physician was “insulted” that patient would consider non-approved therapy | 20            | None                  | 2              | Yes                     |
| 63  | M   | Internet         | Pulmonologist: doubtful of approach but did not advise against participation | 90            | Liposuction painful   | 3              | Yes                     |
| M   |     | Another study participant | Internist: against approach              | Little but welder so environmental exposure | None          | 2.5            | No                      |

PYH: per year history; ASCs: adipose stem cells; ER: emergency room.
Table 2. Study Participant Perceptions of Treatment Effect, Time to Maximal Effect, Loss of Effect, Perspectives on Re-Infusion, and Undirected Comments

| Age | Sex | Smoking (PY) | Time post-infusion at independent interview (months) | Time to optimal subjective effect | Time course of overall effect | Waning of effect over time | Do it again? | Other comments and effects noted (undirected) |
|-----|-----|--------------|------------------------------------------------------|----------------------------------|------------------------------|--------------------------|-------------|---------------------------------------------|
| 72  | M   | 40           | 13                                                   | 1 day                            | Continually getting better   | No                       | Yes         | Lethargy, memory loss, pallor gone, arthritis gone for 2 months, actinic keratosis better, increased sex drive, better hearing, exercises |
| M   | 100 | 17           | 1 month                                              | Continually getting better       | No                           | Yes                      |             | Sounds and looks better                      |
| F   | 75  | 1 month      | Continually getting better                           | No                               | Yes                          |                          |             | Off prednisone                               |
| F   | 70  | 3 months     | Yes                                                  | No (yes if cost-free)            |                              |                          |             | Looks better, no cough, no bronchitis       |
| 70  | M   | 50           | 23                                                   | None                             | None                         | Yes                      | No (yes if cost-free) | Getting worse                               |
| 61  | F   | 40           | 15                                                   | 1 month                          | Continually getting better   | No                       | No (yes if cost-free) | Feels stronger and does not get URIs, but not oxygen-independent which is what was hoped for |
| 73  | F   | 45           | 12                                                   | None                             | None                         | Yes                      | Yes         | Thyroid is better; pulmonologist decreasing thyroid meds 15-20% increase in breathing capabilities initially, now baseline; RLL malignancy discovered after treatment; cough better since treatment |
| F   | 50  | 27           | 1 day                                                | 3 months                         | Yes                          | Yes                      |             |                                             |
| 69  | M   | 60           | 20                                                   | 1 month                          | Gradually getting worse after first month | Yes                      | No (yes if cost-free) | Easier oxygen intake, but no difference |
| 57  | F   | 20 (quit 2009) | instantly                                           | 1 month                          | No                           | Yes                      |             | Also had similar infusions (3) at another (US) facility. Noted that fatigue lessened and post-exertional recovery improved. |
| 63  | M   | 90           | 7                                                    | None                             | None                         | None                     | No          | On UCLA lung transplant program Fewer panic attacks due to SOB, wife noticed patient has been less confused and has had fewer other medical issues; still on oxygen |
| M   | Little but welder so environmental exposure | 18 | 1 day | Continually getting better | None | Yes, if he could receive without travel |             | |

PY: packs per year; UTI: urinary track infection; RLL: right lower lobe; SOB: shortness of breath.
interview data obtained by a distinct set of collaborating investigators who were not involved in the initial protocol design, nor in recruitment or treatment of subjects. This method of collaboration involving independent interviewers was employed to strengthen the data obtained from the telephonic interview process, which involved questions presented in a consistent manner by investigators devoid of economic relationship with either the treatment center or physicians involved in the study. Given that the trial design involved patients traveling from the USA to countries with sovereign regulatory jurisdictions, it was felt helpful to provide this additional, secondary validation.

COPD is a progressively degenerative condition associated with ongoing inflammation, alveolar destruction, and eventual death of the patient. To date, short of lung transplantation, treatment is symptomatic and palliative. The quality of life and lack of progress demands the ethical exploration of novel approaches. Unfortunately, evaluation of stem cell therapy in COPD has lagged behind other areas of regenerative investigation, with only a single clinical trial published to date [6].

The underlying cause of COPD is inflammatory and/or immunologically mediated [15] destruction of alveolar tissue associated with T cell reactivity [16, 17], pathological pulmonary macrophage activation [18], and auto-antibody production [19]. The exploration of SVF as a potential therapeutic approach to COPD is suggested by its content of both mesenchymal stem cells and T regulatory cells, both of which can be purified in high concentrations from adipose stromal vascular tissue together with high concentrations of T regulatory cells [20]. Mesenchymal stem cells have been demonstrated to potently suppress autoreactive T cells [21], inhibit macrophage activation [22], and autoantibody responses [23]. The T regulatory cells derived from adipose tissue have been shown in animal models to be approximately 100 more potent than peripheral T cells at secreting cytokines therapeutic for COPD such as IL-10 [24, 25]. The use of SVF, incorporating both cell types, has yielded promising clinical results in autoimmune conditions such as multiple sclerosis [13]. Administration of BM-MSC into neonatal oxygen-damaged lungs, which manifest COPD-like alveolar dysplasia, has been demonstrated to yield improvements in an animal model [26, 27]. In addition, it is reported that intravenous administration of ASC to mice exposed to cigarette smoke is able to nearly completely ameliorate the smoke-induced emphysema [7].

Plastic surgeons have utilized autologous fat transplantation as a volume filler for decades. Interestingly, early observations suggested that components of autologous liposapirate contain a regenerative fraction. Indeed, the first formal studies on the mononuclear component of liposapirate were reported by Hollenberg and Vost in 1968, who identified the SVF, as the proliferative component of adipose tissue [28]. The cells comprising SVF morphologically resemble fibroblasts and were demonstrated to differentiate into pre-adipocytes and functional adipose tissue in vitro [29, 30]. Although it was suggested that non-adipose differentiation of SVF may occur under specific conditions [31], the notion of “adipose-derived stem cells” was not widely recognized until a seminal paper in 2001, in which Zuk et al demonstrated that SVF contains large numbers of mesenchymal stem cells that could be induced to differentiate into adipogenic, chondrogenic, myogenic, and osteogenic lineages [32]. Following this initial description, the same group reported that after in vitro expansion, the SVF-derived ASC had surface marker phenotype similar to BM-MSC, including the presence of CD29, CD44, CD71, CD90, CD105/SH2, and SH3, and lacking CD31, CD34, and CD45 expression [33]. Since these initial studies, numerous clinical trials have been conducted utilizing SVF cells. For example, the use of purified SVF cells has been performed in breast augmentation surgery to increase efficacy of fat grafting. Yoshimura et al developed a procedure termed “cell-assisted lipotransfer” in which liposapirate is divided equally into two portions: one half used for concentration of cells derived from the SVF component, the other half used primarily to provide volume. The cell-assisted lipotransfer procedure was found to be effective and safe for soft tissue augmentation, and superior to conventional lipoinjection [34]. Currently, several clinical trials have been approved and are ongoing involving infusion of autologous SVF cells for treatment of liver failure, post-infarct remodeling, and ischemic cardiomyopathy among others; these trials are providing safety information concerning SVF infusion to complement the literature involving local SVF injection. In addition, a large set of animal studies as well as early-phase clinical trials have demonstrated the safety of other intravascular or intraparenchymal cell infusions in humans. Bone marrow-derived stem cells have been administered to more than 1,000 cardiac subjects with a clear record of safety as well as some indication of efficacy [35].

It is interesting to note that none of the physicians involved in routine non-study care of these patients initially suggested that they consider a clinical trial involving cells, despite the well-known progressive and inexorable course of their disease. Once the patients learned about the opportunity to participate in the trial, primary care physicians tended to encourage their participation in clinical trials to a greater degree than did specialty physicians (pulmonologists), who typically discouraged study participation.

There are some weaknesses inherent to this method of study and analysis. Because subjects traveled a significant distance to the treatment facility, the study design did not incorporate their return for objective testing in follow-up, and thus the key follow-up data after the initial discharge were obtained by interview and subjective input provided by the subjects. Importantly, in this study model, the protocol anticipated that subjects would obtain additional specific follow-up testing under the care of their local physicians; however, an insufficient number of these studies were ultimately obtained to permit analysis of these data. Accordingly, the results are limited to those focusing on subjective indices of adverse event occurrences as well as quality of life for the subjects. Further, because this study employed a financial model in which subjects funded the costs of the study as well as expending funds for their travel, post-procedural follow-up testing was limited to those approaches which did not add significant costs.

Another weakness may arise from the heterogeneous cellular composition of SVF. The use of this nucleated cell fraction from adipose tissue could theoretically support a more robust therapeutic response, but also could be responsible for inter-patient variability in potency that could lead to future variability of efficacy among individuals. In addition, there has
been no evaluation to date of the bio-activity of SVF or ASCs derived from adipose tissue of patients with COPD vs. SVF or ASCs derived from healthy individuals.

This trial provides the first evidence that the intravenous infusion of autologous SVF immediately following liposuction is feasible and safe in patients with significant COPD. The patients interviewed reported no significant clinical adverse events related to the infusion. This report sets the stage for future evaluations of SVF safety as well as efficacy with additional small phase I-like study designs, as well as larger studies using prospective blinded and randomized design elements.

Conclusions

Here we present results of a 12-subject study that evaluated effects of autologous SVF infusion in the context of moderate to severe COPD. The treatment protocol was performed according to the regulatory specifications of the government of Mexico with jurisdiction over the treatment facility. Independent interviews were conducted by investigators entirely uninvolved in the recruitment and treatment of subjects, to limit investigator bias in tabulation of the interview-based endpoints. The incidence of adverse events was small, and related to the liposuction procedures required for the harvest of adipose tissue. No adverse events related to the cardio and pulmonary systems were observed. The majority of study participants expressed the willingness to receive another infusion if possible, due to a feeling of well-being associated with the infusion. We believe the current study provides an early evidence of feasibility and safety of infusion of manual kit-based SVF preparations into the patients with COPD, and supports the expansion of such an approach into larger prospective clinical trials with objective follow-up measures designed to assess efficacy.

Consent

All patients were consented and agreed to participate in the study, and have their data published.

Competing Interests

KC is an officer of US Stem Cell, Inc. JL is director of the Regenerative Medicine Institute, where subjects were treated. JP and JL are employees of the Regenerative Medicine Institute.

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Author Contributions

KC provided protocols and procedures for processing of adipose tissue to SVF. TI, JL, and RC were responsible for clinical procedures and follow up of patients. All authors read and approved the final manuscript.

Abbreviations

SVF: stromal vascular fraction; COPD: chronic obstructive pulmonary disease; ASCs: adipose stem/stromal cells; MSC: mesenchymal stem cell; SAE: severe adverse event

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