Stem Cell Therapy for Lung Disease*

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DESCRIPTION

Lung disease remains a significant cause of morbidity and mortality worldwide in which currently there is no cure. The use of stem cell products including mesenchymal stem cells (MSCs) (mesenchymal stromal cells) from bone marrow (BM), adipose tissue (fat), myocytes (muscle) or peripheral blood, alone or in combination with platelet-derived products (e.g. platelet-rich plasma, lysate) are being investigated in the treatment of lung disease including but not limited to chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), acute respiratory distress syndrome (ARDS), pulmonary hypertension, and bronchopulmonary dysplasia.

Mesenchymal stem cells (MSCs) are multipotent stromal cells that can differentiate into a variety of cell types, including osteoblasts (bone cells), chondrocytes (cartilage cells), myocytes (muscle cells) and adipocytes (fat cells that give rise to marrow adipose tissue). Mesenchymal stem cells (MSCs) have immunomodulatory properties and secrete cytokines. MSCs remain in a quiescent (non-proliferative) state during most of their lifetime, pending stimulation by the signals triggered by tissue renewal, damage, and

remodeling processes. Because of their multi-lineage potential, immunomodulatory properties, and ability to secrete anti-inflammatory molecules, MSCs may have the potential to treat various chronic autoimmune, inflammatory and degenerative diseases. MSCs have been isolated from various sites, including dermis, amniotic fluid, adipose tissue, endometrium, dental tissue, synovial fluid, placenta and umbilical cord tissue, however, bone marrow derived MSCs are considered the preferred source for bone repair and regeneration as there is better chondrogenic differentiation potential and have been identified as currently the primary source of procurement.

Harvesting the mesenchymal stem cells is performed by withdrawing bone marrow (BM), adipose tissue (fat), peripheral blood, or MSCs from another site. The harvested cells are isolated and concentrated, and along with platelet-rich plasma, and the MSCs are then reintroduced into the body and enter the pulmonary vasculature (vessels of the lungs) where cells are trapped in the microcirculation (i.e., the "pulmonary trap"). Alternatively, nebulized stem cells are reintroduced through the airways in patients who have undergone an adipose (fat tissue) treatment. Recent studies have demonstrated that mesenchymal stem cells modulate the immune response and may reduce lung injury.

Acute Respiratory Distress Syndrome (ARDS)

Acute respiratory distress syndrome (ARDS) is a major cause of respiratory failure and is often associated with multiple organ failure. Clinical disorders such as pneumonia, sepsis, aspiration of gastric contents, and major trauma can precipitate ARDS. The pathogenesis of ARDS involves lung endothelial injury, alveolar epithelial injury, and the accumulation of protein-rich fluid and cellular debris in the alveolar space. Even with current advances in lung-protective ventilation and fluid management, patient mortality rate remains high. A clinical diagnosis of ARDS is associated with large financial burdens due to long hospitalization and ICU stays, a poor survival rate, and an increased use of health services after hospital discharge. Most patients who survive an episode of ARDS will sustain some degree of permanent physical disability as well as reduction in their quality of life. To decrease the occurrence of these life-changing consequences, alternative therapeutic options are needed that can reduce lung injury while facilitating and enhancing lung repair. Mesenchymal stem cells (MSCs) are being investigated as a treatment modality for ARDS.

(2015) Wilson et al reported-on stem cells for ARDS Treatment (START) trial a multicenter, open-label, dose-escalation, phase 1 clinical trial, aimed to test the safety of a single dose of allogeneic bone marrow-derived MSCs in patients with moderate-to-severe ARDS (acute respiratory distress syndrome). Patients were enrolled in the intensive care units at University of California, San Francisco, CA; Stanford University, Stanford, CA; and Massachusetts General Hospital, Boston, MA, between July 8, 2013, and Jan 13, 2014. Patients were included if they had moderate-to-severe ARDS as defined by the acute onset of the need for positive pressure ventilation by an endotracheal or tracheal tube, a PaO2:FiO2 less than 200 mm Hg with at least 8 cm H2O positive end-expiratory airway pressure (PEEP), and bilateral infiltrates consistent with pulmonary edema on frontal chest radiograph. The first three patients were treated with low dose

MSCs (1 million cells/kg predicted bodyweight [PBW]), the next three patients received intermediate dose MSCs (5 million cells/kg PBW), and the final three patients received high dose MSCs (10 million cells/kg PBW). Primary outcomes included the incidence of pre-specified infusion associated events and serious adverse events. Secondary outcomes included standard respiratory and systemic endpoints, 28- and 60-day mortality, and measurement of biologic markers of inflammation and endothelial and epithelial injury. There was no pre-specified infusion associated events or treatment related adverse events in any of the nine patients in this trial. Serious adverse events (SAEs) were subsequently observed in three patients in the weeks following the infusion: two patients expired > seven days after the MSC infusion, and one patient was discovered to have multiple embolic infarcts of the spleen, kidneys, and brain that were age-indeterminate but thought to have occurred prior to the MSC infusion based on the MRI results. None of these SAEs were thought to be MSC-related. The mean lung injury score declined (improved) between the baseline and day three in all three dosing groups. Numerically, the greatest decrease in lung injury score (LIS) was observed in the high dose cohort and the smallest decrease was observed in the low dose cohort (high dose 2.9 to 1.6 (-45%), intermediate dose 2.8 to 1.8 (-36%), low dose 3 to 2.1 (-30%)), though these differences between groups were not statistically significant (p=08720). None of the patients received rescue therapies for refractory hypoxemia. Mean SOFA (sequential organ failure assessment) declined in all three dosing groups over the first three days. As with LIS, the greatest numerical decline was observed in the high dose cohort and the smallest decrease was observed in the low dose cohort (high dose 7 to 3.7 (-48%), intermediate dose 8.7 to 6.7 (-23%), low dose 8 to 7.7 (-4%)). The difference among groups was not statistically significant (p=0.7653). Median levels of biomarkers IL-6, IL-8, RAGE, and Ang-2 levels declined between baseline and day three. There were no significant differences in the magnitude of decline among groups for any of the biomarkers (p=0.3679, 0.3189, 0.3189, and 0.8669, respectively). Limitation of this study is the small sample size, and the study did not draw conclusion about either the efficacy or long-term safety of MSCs for ARDS. The authors concluded, a single intravenous MSC infusion of up to 10 million cells/kg PBW was well tolerated in patients with moderate to severe ARDS in this phase one trial. There were no serious adverse events related to MSC administration after six months of follow-up. We are currently conducting a randomized, double-blind placebo-controlled phase two clinical trial of 10 million MSCs/kg PBW in 60 patients with moderate to severe ARDS, with a primary focus on safety and secondary outcomes including respiratory, systemic and biologic endpoints.

(2014) Zheng et al examined the safety and efficacy of allogenic adipose-derived mesenchymal stem cells (MSCs) in the treatment of acute respiratory distress syndrome (ARDS) in a randomized, placebo-controlled pilot study. Twelve adult patients meeting the Berlin definition of acute respiratory distress syndrome with a PaO_2/FiO_2 ration < 200 were randomized to receive allogeneic adipose-derived MSCs or placebo in a 1:1 fashion. Patients received one intravenous dose of 1×10^6 cells/kg of body weight or saline. Possible side effects were monitored after treatment. Acute lung injury biomarkers, including IL-6, Il-8 and surfactant protein D (SP-D), were examined to determine the effects of MSCs on lung injury and inflammation. There were no infusion toxicities or

serious adverse events related to MSCs administration and there were no significant differences in the overall number of adverse events between the two groups. Length of hospital stay, ventilator-free days and ICU free days at day 28 after treatment were similar. There were no changes in biomarkers examined in the placebo group. In the MSCs group, serum SP-D levels at day 5 were significantly lower than those at day 0 (p=02.027) while the changes in IL-8 levels were not significant. The IL-6 levels at day 5 showed a trend towards lower levels as compared with day 0, but this trend was not statistically significant (p=0.06). The authors concluded, due to the small sample size, only limited effects can be observed in this preliminary study. Nevertheless, the findings demonstrated that infusion of allogeneic adipose-derived MSCs was safe and there were no significant adverse events related to the MSCs in ARDS. The change in ARDS biomarker, SP-D, after treatment may suggest the protective effect of MSCs. However, additional larger studies with a longer follow-up period is necessary to confirm the safety and efficacy profile of MSCs in ARDS and to establish the best strategy for their administration, including concomitant medication and dosage.

Summary of Evidence
Based on review of the peer reviewed medical literature the evidence is limited. Two randomized controlled trials examined the safety and efficacy of allogenic adipose-derived mesenchymal stem cells (MSCs) and allogeneic bone marrow-derived mesenchymal stem cells (MSCs) in patients with acute respiratory distress syndrome (ARDS). The findings demonstrated that infusion of MSCs was safe and there were no significant adverse events related to the MSCs in ARDS. The change in ARDS biomarkers after treatment may suggest the protective effect of MSCs. However, additional large studies with longer follow-up periods are necessary to confirm the safety and efficacy profile of MSCs in ARDS and to establish the best strategy for their administration, including concomitant medication and dosage. The evidence is insufficient to determine the effects of this technology on net health outcomes.

Bronchopulmonary Dysplasia (BPD)
(2019) Bronchopulmonary dysplasia (BPD) remains a major contributor to mortality and morbidity in infants born prematurely, and current strategies to prevent this disease have been only moderately successful. BPD is a multifactorial disease where none of the current treatment strategies has effectively decreased complications in BPD survivors. Over the past years, the interest in using mesenchymal stem cell (MSC)-based therapies to treat BPD has increased especially in response to findings in pre-clinical studies demonstrating positive benefits (Augustine et al and Nitikin et al).

Currently, there are several clinical trials for BPD registered as completed or active on ClinicalTrials.gov. The first published trial using MSCs to treat infants with BPD was a phase 1, dose-escalation trial (NCT01297205) using umbilical cord blood–derived MSCs at a concentration of 1×107 or 2×107 cells per kg. This study demonstrated that the treatment was well tolerated in patients with BPD and that the levels of IL-6, IL-8, MMP-9, TNF-α, and TGF-β in tracheal aspirates were significantly reduced compared with baseline values. A 2-year follow-up study of this trial (NCT01632475) was published in

(2017) revealing that although one infant in the MSC group died suffering from Enterobacter cloacae sepsis, the remaining 8 infants showed no sign of transplant-related adverse outcomes or tumorigenicity was observed. In addition, this follow-up study reported decreased need for supplemental oxygen at discharge compared with the control group; however, larger trials are needed to prove efficacy. The same investigators are currently running a 5-year follow-up study of the NCT01297205 trial (NCT02023788) as well as a phase 2 study (NCT01828957). Moreover, there is one additional clinical trial listed on ClinicalTrial.gov as completed (NCT02381366); however, there are no results yet published on the PubMed database from this trial. Taken together, the enthusiasm for MSC-based strategies for treatment of premature infants with BPD is currently increasing and at present, there are nine clinical trials recruiting patients.

Summary of Evidence
Mesenchymal stem cell (MSC) therapies for the treatment of bronchopulmonary dysplasia (BPD) may demonstrate promising results in experimental lung models, however, this has not translated into significant improved clinical outcomes in patients to date. While current clinical trials may demonstrate that MSC therapies are safe for lung disease patients, no significant efficacy or improved lung function has currently been demonstrated. Further clinical trials are needed to include revealing the in vivo mechanism of action and selecting the patient group most likely to respond. The evidence is insufficient to determine the effects of this technology on net health outcomes.

Chronic Obstructive Pulmonary Disease (COPD)
Chronic obstructive pulmonary disease (COPD) is a progressive lung disorder that occurs as result of prolonged cigarette smoking, second-hand smoke, and polluted air or working conditions. COPD is the most prevalent form of chronic lung disease. The symptoms of COPD include shortness of breath (dyspnea), cough, and sputum production, exercise intolerance and reduced quality of life (QOL). These signs and symptoms are brought about by chronic inflammation of the airways, which restricts breathing. When fibrotic tissues contract, the lumen is narrowed, compromising lung function. As histological studies confirm, airway fibrosis and luminal narrowing are major features that lead to airflow limitation in COPD.

Chronic obstructive pulmonary disease (COPD) is a serious global health issue, with a prevalence of 9-10% of adults aged 40 and older, and the prevalence of the disease is only expected to rise. Currently COPD accounts for 27% of tobacco related deaths and is anticipated to become the fourth leading cause of death worldwide by 2030. COPD effects approximately 600 million individuals roughly 5% of the world's population. Despite modern medicine and technological advancements, there is no known cure for COPD.

The difficulty in treating COPD and other lung diseases rests in the trouble of stimulating alveolar wall formation. Treatment has been limited by two things: a lack of understanding of the pathophysiology of these disease processes on a molecular level and a lack of pharmaceutical development that would affect these molecular mechanisms.

Treatment is focused primarily on addressing the symptoms of the disease rather than healing or slowing the progression of the disease itself.

There are few options available outside bronchodilators and corticosteroids. Although lung transplants are performed as an alternative option, there is currently a severe shortage of donor lungs, leaving many patients to die on waiting lists prior to transplantation. Lung transplantation is also a very invasive form of treatment with a 5-year mortality rate of approximately 50% and is also associated with lifelong immunosuppression. Stem cell therapy using mesenchymal stem cells (mesenchymal stromal cells) is being utilized and studied in the treatment of COPD.

The Lung Institute provides treatment for COPD using autologous stem cells (mesenchymal stromal [stem] cells). Coleman reported on a pilot study of individuals diagnosed with COPD that were tracked by the Lung Institute to measure the effects of treatment via either venous protocol or adipose protocol (nebulizer) on both their pulmonary function, as well as their quality of life (QOL). All pulmonary function tests (PFTs) were performed according to national practice guideline standards for repeatability and acceptability. On the PFTs, the pre-treatment data was collected through on-site testing or through previous medical examinations by the patient's primary physician (if done within in two weeks). The test was repeated by their primary physician 6 months after treatment (due to the examination information required from the primary physicians, only 25 out of the 100 patients are reflected in the PFT data). On the quality-of-life testing, data was collected through the implementation of the Clinical COPD Questionnaire (CCQ) based survey. The survey measured the patient's self-assessed quality of life on a 0-6 scale, with adverse quality of life (QOL) correlated in ascending numerical order. It was implemented in three stages: pretreatment, 3 months post-treatment, and 6 months post-treatment. The survey measured two distinct outcomes: the quality-of-life score (QLS) and quality improvement score (QIS), a percentage-based measurement determining the proportion of patients within the sample that experienced QLS score improvement.

Over the duration of six months, results of 100 patients treated for COPD through venous and adipose based therapies were tracked by the Lung Institute in order to measure changes in pulmonary function and any improvement in quality of life. Of the 100 patients treated by the Lung Institute, 64 were male (64%) and 36 were female (36%). Ages of those treated ranged from 55-88 years of age with an average age of 71. Throughout the study, 82 (82%) were treated with venous derived stem cells, while 18 (18%) were treated from stem cells derived from adipose tissue. Over the course of the study, the patient group averaged an increase of 35.5% to their Quality of Life (QLS) score within three months of treatment. While in the QIS, 84% of all patients found that their QOL score had improved within three months of treatment. Within the PFT results, 48% of patients tested saw an increase of over 10% to their original pulmonary function with an average increase of 16%. During the three to six-month period after treatment, patients saw a small decline in their progress, with QLS scores dropping from 35% to 32%, and QIS from 84% to 77%. The author concluded, although more studies using a

greater number of patients is needed to further examine objective parameters such as PFTs, exercise tests, oxygen, medication use and hospital visits, larger sample sizes will also help determine if one protocol is more beneficial than others. With deeper research, utilizing economic analysis along with long-term follow up will answer questions on patient selection, the benefits of repeated treatments, and a possible reduction in healthcare costs for COPD treatment.

(2018) Sun et al summarized the progress made by regenerative therapies for COPD by analyzing results from both pre-clinical studies and completed clinical trials. Clinical results from completed clinical trials include NCT00683722 (see below Weiss et. al 2013), NCT01110252, and NCT01306513. The clinical trial (NCT01110252) applied autologous bone marrow mononuclear cells (BMMCs) in COPD patients and was performed between 2009 and 2011. BMMCs are heterogenous cells that include lymphocytes, monocytes, hematopoietic progenitor cells (HPCs), and MSCs. Four patients with severe COPD were recruited. Their bone marrows were harvested separately and processed to separate out mononuclear cells (BMMCs); these fresh cells were infused back into the patients in a single infusion. No side effects were reported. Pulmonary function tests were performed over the next two years. Two of the four patients had a satisfactory performance with an increased FEV1 compared to the predicted values, suggesting a decrease air trapping and an increase in elasticity. The authors noted that the relatively improved pulmonary function may be due to the anti-inflammation effects based on reported pre-clinical investigations and the first reported clinical trial (NCT00683722). The clinical trial (NCT01306513) was an open-label, non-randomized, non-blind, and prospective phase I clinical trial. The trial was performed between 2010 and 2012. Bone marrows were collected from seven severe to very severe COPD patients while having the first lung volume reduction surgery (LVRS) and were cultured ex vivo to obtain BM-MSCs. Two infusions of autologous BM-MSCs were given to the patients at 6-10 weeks after LVRS, and then a week later after the first infusion. All patients had a second LVRS at 3 weeks after the second infusion of BM-MSCs. No toxicity was observed related to infusions of BM-MSCs. One year after the second LVRS, the FEV1 and body weight increased significantly, lung densitometry also changed significantly among all patients compared with that before the first LVRS. But these changes were comparable to previous reports of patients only had LVRS, indicating the improved pulmonary structures, function and body weight resulted from LVRS rather than BM-MSCs. In summary this study showed the safety and feasibility of autologous BM-MSCs in severe and very severe COPD patients. However, because no control group was included, it cannot be concluded whether the changes of FEV1, body weight, lung densitometry and expression of CD3 were affected by LVRS or/and BM-MSCs.

(2013) Weiss et al reported on a placebo-controlled, randomized trial to assess the safety and evaluate the potential efficacy of systemic mesenchymal stem cells in patients with moderate to severe chronic obstructive pulmonary disease (COPD). Sixty-two patients at six sites were randomized to double blinded IV infusions of either allogenic mesenchymal stem cells (MSCs) (Prochymal; Osiris Therapeutics, Inc.) or placebo (vehicle) control treatment groups. Prochymal is an investigational agent containing ex-

vivo-cultured MSCs derived from the bone marrow of healthy adult donors and has demonstrated a strong safety record in previous clinical investigations. Eligible patients were 40 to 80 years of age with moderate to severe COPD, smoking history of > 10 packs-years (current or former smokers), post-bronchodilator FEV^1/FVC ratio < 70%, and post-bronchodilator FEV^1 between 30% and 70% of predicted value. Treatment was administered on days 0, 30, 60 and 90, patients received four monthly infusions (100 x 10^6 cells/infusion). Patients treated with placebo received an infusion of vehicle of the same volume as the MSC infusion. Each infusion took approximately 1 hour to complete. Patients were subsequently followed for 2 years after the first infusion. End points included comprehensive safety evaluation, pulmonary function testing (PFT) and quality of life (QOL) indicators including questionnaires, 6MWT (6-minute walk test) and assessment of systemic inflammation. All patients in both treatment groups received all four scheduled study infusions and no patient discontinued due to study related adverse events (AEs). Nineteen of 30 patients (63%) in the MSC group and 27 of 32 (84%) in the placebo group completed the full protocol. There were no infusional toxicities and no deaths or serious adverse events deemed related to MSC administration. No statistically significant differences in FEV^1, or FEV^1% predicted or observed through 2 years nor were their observed differences between the groups in FVC, FVC% predicted, total lung capacity, or carbon monoxide diffusing capacity from baseline to 1 year or 2 years. No statistically significant or clinically meaningful differences between the two treatment groups were observed in the 6MWT, St. George's Respiratory Questionnaire, or Borg Dyspnea Scale scores (post-test minus pretest) from day 10 to 2 years, or in the physician's global assessments. There were no significant differences in oxygen saturations between the study groups during the 6MWTs during the study visits. There was no significant difference in the number of patients with COPD exacerbations (20 [66.7%] in the MSC group versus 15 [46.9%] in the placebo group). Only a small number of patients were hospitalized for COPD exacerbations during the study protocol (six in the MSC group versus five in the placebo group), and no meaningful comparison could be made. Median time to the first exacerbation was 6.7 months in the MSC group; and could not be estimated for the placebo group due to the smaller number of patients reporting exacerbations. At 1 and 2 years, the probability of being exacerbation free was 46.0% and 31.9%, respectively, in the MSC group versus 56.3% and 52.7%, respectively, in the placebo group. However, the confidence interval (CI) around the probabilities of being exacerbation free at both visits overlapped for the two groups, indicating that the differences were not statistically significant. A review of the patient's diaries revealed that reliever/rescue medication use was not systematically recorded, and it was not possible to do the planned analysis. No significant effects of MSC infusions were observed on pulmonary function or QOL indicators. The authors conclude further large-scale trials will be necessary to more fully examine potential effects of MSCs in patients with COPD and other lung diseases.

In summary, the authors concluded the few preliminary clinical trials reported have been unsuccessful, which has weakened the potential for applying MSCs in COPD patients. Further clinical trials designed to use BM-MCSs (bone marrow mesenchymal stem cells) or AD-MSCs (adipose mesenchymal stem cells) to treat COPD have been registered but

have not yet been started. The three currently reported clinical trials recruited moderate, severe, or very severe COPD patients. The authors of the first clinical trial Weiss et. al. (NCT00683722) stated that the COPD stages of the patients may be the major cause of failure. They also noted that the damage to the pulmonary structures might be too severe to be reversed by the few transplanted MSCs. Further research is needed to investigate how to enhance the engraftment of exogenous MSCs in the damaged lung, determining parameters related to the cells i.e., the dosing of cells, dosing methods and frequency of dosing. Also, more effort should also be given to the design of new trials including study endpoints, age, status and scale of patient cases and the inclusion of proper control groups.

Summary of Evidence
Based on review of the peer reviewed medical literature the literature includes a pilot study by the Lung Institute and three randomized clinical trials on the use of mesenchymal stem cells (MSCs) in the treatment of chronic obstructive pulmonary disease (COPD). The three currently reported clinical trials recruited moderate, severe or very severe COPD patients. The authors of the first clinical trial Weiss et. al. (NCT00683722) stated that the COPD stages of the patients may be the major cause of failure. They also noted that the damage to the pulmonary structures might be too severe to be reversed by the few transplanted MSCs. Further research is needed to investigate how to enhance the engraftment of exogenous MSCs in the damaged lung, determining parameters related to the cells i.e., the dosing of cells, dosing methods and frequency of dosing. Also, more effort should also be given to the design of new trials including study endpoints, age, status and scale of patient cases and the inclusion of proper control groups. The COPD Foundation position statement includes the following: Autologous stem cell therapy is not currently recommended for the treatment of COPD. The COPD Foundation does not recommend the use of autologous stem cell therapy in the treatment of COPD or other lung disease until there is more rigorous scientific and medical proof of its effectiveness. Instead, the COPD Foundation encourages individuals to participate in clinical trials that test the development and potential benefit of this technique. The evidence is insufficient to determine the effects of this technology on net health outcomes.

Idiopathic Pulmonary Fibrosis (IPF)
Idiopathic pulmonary fibrosis (IPF) is a type of interstitial lung disease, which causes progressive scarring, leading to the lung tissue thickening and stiffening. In particular, it affects the interstitium, or the area between the alveoli where gas exchange takes place in the lungs, and the blood vessels. The scar tissue reduces lung capacity and restricts gas exchange, resulting in less oxygen being transferred to the blood.

The exact mechanism through which IPF can cause pulmonary hypertension is not well understood, but it is through which IPF can cause pulmonary hypertension is not well understood, but it is thought that the scarring restricts blood vessels, impeding blood flow and making it more difficult for the heart to pump blood through the lungs. Another theory is that the damage response and resulting scare tissue reactivates pathways

involved in lung development and triggers vascular remodeling. This can change the shape of the blood vessels, such as causing them to narrow and restrict blood flow.

IPF is a debilitating and fatal condition, and while current therapies can help to improve survival and quality of life, there is no known cure. However, research into promising approaches like stem cell therapy is ongoing. Mesenchymal stem cells (MSCs) are now being investigated to treat IPF due to their ability to potentially reduce inflammation in the lungs. Damage caused by inflammation can lead to scarring in the lungs, so reducing lung inflammation may be able to lessen further scarring.

(2017) Glassberg et al reported on a phase I randomized and blinded, placebo-controlled clinical trial called AETHER, Allogeneic Human Cells (hMSC) in patients with Idiopathic Pulmonary Fibrosis via Intravenous Delivery trial, which was designed to evaluate the safety of a single infusion of bone marrow derived mesenchymal stem cells in patients with idiopathic pulmonary fibrosis (IPF). The study was conducted at the University of Miami Miller School of Medicine (Miami, FL). Eligible patients were between the ages of 40 and 90, had a diagnosis of IPF according to the American Thoracic Society Guidelines, an FVC of at least 50% of predicted and a diffusing capacity of the lungs for carbon monoxide (DLCO) of at least 30% predicted. Nine patients with mild to moderate IPF were sequentially assigned to 1 of 3 cohorts and dosed with a single IV infusion of 20, 100, or 200 x 10^6 human bone marrow derived mesenchymal stem cells per infusion from young, unrelated, men. All baseline patient data were reviewed by a multidisciplinary study team to ensure accurate diagnosis. The primary end point was the incidence (at week 4 post-infusion) of treatment-emergent serious adverse events, defined as the component of death, nonfatal pulmonary embolism, stroke, hospitalization for worsening dyspnea, and clinically significant laboratory test abnormalities. Safety was assessed until week 60 and additionally 28 days thereafter. Secondary efficacy end points were exploratory and measured disease progression. No treatment emergent serious adverse effects were reported. Two non-treatment-related deaths occurred because of progression of IPF (disease worsening and/or acute exacerbation). By 60 weeks post-infusion, there was a 3.0% mean decline in the percent predicted FVC and 5.4% mean decline in percent predicted diffusing capacity of the lungs for carbon monoxide (DLCO). Limitations of this study included its small sample size, lack of randomization, and lack of a placebo arm. The authors concluded, data from the trial support the safety of a single infusion of human mesenchymal stem cells in patients with mild-moderate IPF. However, larger randomized placebo-controlled studies are needed to evaluate efficacy. Further studies should be conducted with larger numbers of patients as well as patients with more advanced IPF. One challenge will be to establish the optimal number of infusions and the appropriate dosing interval. Another challenge will be to identify the early-stage patients most likely to benefit from the intervention. Ultimately, well-designed, and meticulously conducted phase II/III clinical trials of hMSCs for the treatment of IPF will be required to evaluate their efficacy as a potential therapeutic modality for this devastating disease.

Summary of Evidence
Based on review of the peer reviewed medical literature the evidence is limited. A phase I randomized and blinded, placebo-controlled clinical trial called AETHER, Allogeneic Human Cells (hMSC) in patients with Idiopathic Pulmonary Fibrosis via Intravenous Delivery trial, which was designed to evaluate the safety of a single infusion of bone marrow derived mesenchymal stem cells in patients with idiopathic pulmonary fibrosis (IPF). This trial supported the safety of a single infusion of human mesenchymal stem cells in patients with mild-moderate IPF. However, larger randomized placebo-controlled studies are needed to evaluate efficacy. Further studies should be conducted with larger numbers of patients as well as patients with more advanced IPF. One challenge will be to establish the optimal number of infusions and the appropriate dosing interval. Another challenge will be to identify the early-stage patients most likely to benefit from the intervention. Ultimately, well-designed and meticulously conducted phase II/III clinical trials of hMSCs for the treatment of IPF will be required to evaluate their efficacy as a potential therapeutic modality for this devastating disease. The evidence is insufficient to determine the effects of this technology on net health outcomes.

Pulmonary Hypertension
Pulmonary hypertension is a type of high blood pressure that affects the arteries in the lungs and the right side of the heart. With pulmonary hypertension the tiny arteries in the lungs called pulmonary arterioles and capillaries become narrowed, blocked, or destroyed which makes it harder for blood to flow through the lungs and raises pressure within the lungs' arteries. As the pressure builds, the hearts lower chamber (right ventricle) must work harder to pump blood through the lungs which eventually causes the heart muscle to weaken and fail. Pulmonary hypertension cannot be cured, and treatment can help lessen symptoms and improve quality of life. Current treatment of pulmonary hypertension includes medications, oxygen therapy, and surgery (atrial septostomy or transplantation). Stem cell therapies are being investigated in the treatment of pulmonary hypertension.

Pulmonary hypertension is classified into five groups depending on the cause:

- Pulmonary arterial hypertension
- Pulmonary hypertension caused by left-sided heart disease
- Pulmonary hypertension caused by lung disease
    - Chronic obstructive pulmonary disease (COPD), such as emphysema
    - Pulmonary fibrosis
    - Sleep apnea and other sleep disorders
    - Long term exposure to high altitudes
- Pulmonary hypertension caused by chronic blood clots
- Pulmonary hypertension associated with other conditions that have unclear reasons why the pulmonary hypertension occurs

Summary of Evidence
Based on review of the medical literature there is limited evidence regarding stem cell therapy for the treatment of pulmonary hypertension which have focused on pulmonary vascular disease. The literature includes case series and multicenter trials. Stem cell

therapies in animal models are proving to be promising therapies, however, the results in recent multicenter trials with humans have been mixed. Encouraging results have been published that highlight the feasibility, safety and efficiency of such therapeutic approaches, however, further studies are needed to evaluate stem cell therapy as an established therapy prior to transplantation to treat patients with pulmonary hypertension. The Pulmonary Hypertension Association (PHA) states the following regarding the use of stem cells in the treatment of pulmonary hypertension: Stem cell use has not been adequately studied and neither the efficacy nor safety of stem cells to treat pulmonary arterial hypertension (PAH) has been established. Currently, the Scientific Leadership Council (SLC) recommends stem cell therapy only as part of a registered, clinical trial in carefully selected patients. We recommend that patients discuss stem cell therapy (and any new therapies) with their PH specialist. The evidence is insufficient to determine the effects of this technology on net health outcomes.

Policy Guidelines and Position Statements

American Lung Association (ALA)
(2016, Reaffirmed in 2021) The American Lung Association provided a statement on stem cell therapy for lung disease that included the following:

The use of stem cells for treating lung diseases has great appeal. As we learn more about the therapeutic potential of stem cells and other cell therapies in clinical trials of non-lung diseases, we hope to be able to move toward further consideration of these approaches in lung diseases.

However, as yet, there is very little known about the short and long-term effects of administering any type of stem cell therapy to patients with lung diseases. Until we know more, we are strongly concerned that the treatment could cause adverse effects and could worsen the patient's condition.

You may come across information on the internet or other sources about stem cells being administered to patients with lung diseases, such as emphysema, pulmonary hypertension or pulmonary fibrosis. We caution all patients to carefully consider the claims of benefit being made by many of these programs as they have not been substantiated or reviewed by experts in the field or any regulatory agency. We understand that patients may be attracted to these therapies because they have severe, irreversible disease and are under great stress. Although we understand this motivation, we still advise against the use of these unproven and often expensive therapies.

Because of the potential for harm, the lack of any proven benefit, and the high fees that many of these programs charge, we caution you not to participate in these or any other unauthorized or unapproved stem cell administrations, unless independent credible, reliable, and objective sources of information are available to substantiate the information and claims being made.

Additionally, the Food and Drug Administration recently issued draft guidelines clarifying that stem cells are considered drugs and need to be reviewed through a rigorous approval process before being used in patients.

At present, there are only a small number of approved clinical trials in the United States and Canada investigating cell therapy approaches for lung diseases. These can be found on the website of the National Institutes of Health at clinicaltrial.gov. We are hopeful there will be more in the future.

The American Lung Association has recently signed onto a statement along with a number of respiratory and thoracic societies, outlining the potential dangers and risks in using unregulated stem cell treatments for respiratory diseases. *(Accessed January 2022*)

American Thoracic Society (ATS)

1. (2017) The American Thoracic Society issued public information/information series regarding unproven stem cell treatments for lung disease that included the following:

- **Are Stem cell treatments an option for lung disease?**
  - In theory, yes in the future. In many lung diseases, cells that make up the respiratory system are either lost or do not function properly. A stem cell treatment that restores lung cell function might be able to reverse or even cure some lung diseases. As of now, there are no proven stem cell treatments for any lung disease.

- **What is an unproven stem cell treatment?**
  - Unproven stem cell treatments are those that have not yet been adequately or fully tested for safety and effectiveness (how well they work). The best way to test potential stem cell therapies is through clinical research trials that have to follow certain rules. These rules are set by national regulatory agencies such as the FDA (Food and Drug Administration) to make sure that the treatments are tested following proper scientific methods without any conflict of interest.

- **Who offers unproven stem cell treatments?**
  - Unfortunately, there are hundreds of clinics and other groups offering unproven stem cell treatments in the United States. A frequent method that they use to treat lung disease involves removing cells from the person's fat or bone marrow and given the cells back to the person through his or her bloodstream. These approaches have not been proven to work and are not FDA regulated or approved as accepted treatments for any type of lung disease. This means that the necessary clinical research trials to make sure that these treatments are safe and effective have not been done. Unfortunately, this does not prevent them from being offered despite unknown risk or benefit.

- **Do unproven stem cell treatments work for lung disease?**

- There have been promising studies in animal models of lung diseases. Yet, there is no reliable evidence that stem cell treatments are effective for any lung disease. To date, there have been some legitimate clinical trials, approve and regulated by the FDA or by appropriate regulatory agencies in other countries. These have been done for a number of lung diseases including COPD, acute respiratory distress syndrome, idiopathic pulmonary fibrosis and pulmonary hypertension. These studies have used several different types of stem cells including mesenchymal stromal cells and endothelial progenitor cells. Initial results suggest that the stem cells used appear to be safe over a short-term period. However, further follow-up is necessary to ensure long term safety. Importantly, none of these studies have shown any beneficial effect in any lung disease tested so far.

- **Could unproven stem cell treatments be harmful?**
  - Yes, these treatments can be potentially harmful. Potential risks include cell embolism (stem cells clotting in the lungs) and the cells causing abnormal growth including tumors. In addition, a number of clinics are giving treatment in ways that do not meet normal standards of sterility (to prevent infection) and safety.

- **What do pulmonologists say about unproven stem cell treatments?**
  - Pulmonologists (lung specialists) familiar with the issues of unproven stem cell therapies for lung diseases are opposed to this approach. However, many lung specialists are not yet familiar with the field. The American Thoracic Society (ATS) Stem Cell Working Group as well as other professional societies have developed educational resources for doctors as well as for patients and their families. All involved are strongly encouraged to read these resources to learn more about stem cells and their use. Patients and doctors should take time to learn all they can about the issues surrounding unproven stem cell therapies.

- **What do lung disease foundations and patient's advocacy groups say about unproven stem cell treatments?**
  - A growing number of national and international respiratory disease societies and patient advocacy groups have taken strong positions against unproven stem cell therapies. This is also true for the leading stem cell scientific societies who do not support use of unproven stem cell therapies at this time. All these groups are trying to educate patients, families, caregivers, and health care professionals about the potential dangers of unproven stem cell treatments. In the U.S., these foundations include the Alpha-1 Foundation, American Lung Association (ALA), COPD Foundation, Cystic Fibrosis Foundation, Pulmonary Fibrosis Foundation, and the Pulmonary Hypertension Association. None of these groups believes there is enough known about stem cell therapies to use them in lung disease without more research.

(*Accessed January 2022*)

2. (2016) The American Thoracic Society issued a statement on unproven stem cell interventions for lung disease which included the following:

   A central component of the mission of medical societies is to translate new scientific information into patient education. The undersigned lung, respiratory, and thoracic societies, and patient advocacy groups strongly believe that patients and their families along with the general public should have at their disposal unbiased and scientifically sound information on new potential therapeutic options including stem cell-based treatments.

   Continuing advances in stem cell biology have created justified excitement at the prospect of personalized stem cell-based therapies through the use of clinically relevant cell populations. We recognize the enormous potential of stem cells for disease management including acute and chronic ailments of the respiratory system. As we learn more about the therapeutic potential of stem cells and other cell therapies in clinical trials of non-lung diseases and in initial trials in lung diseases, we hope to move towards further consideration and potential implementation of these approaches.

   However, as with all medical interventions, patient safety must be the top priority of any prospective stem cell-based therapy or treatment. As yet, there is very little known about the short- and long-term effects in terms of safety and efficacy of administering any type of stem cell-based therapy to patients with lung diseases. Until we know more, we must be strongly concerned that the treatment could cause adverse effects and could worsen the patient's condition rather than improve it.

   At present, there are only a small number of peer reviewed and appropriately regulated approved clinical trials in the United States, Canada, the European Union, Brazil, Asia and Australia investigating cell therapy approaches for lung diseases.

   Thus, we are particularly wary of the ever-increasing examples of direct-to-consumer advertising of untested, unapproved, and potentially dangerous “stem-cell” treatments that take place in several countries. One may come across information on the internet or other sources about stem cells being administered to patients with lung diseases such as emphysema, pulmonary hypertension, cystic fibrosis, or pulmonary fibrosis in several locations worldwide including the United States. We fully acknowledge that patients with severe irreversible lung diseases are under extreme physical and emotional distress that provide the motivation to resort to expensive unproven treatments. Nevertheless, we strongly caution all patients that the claims of benefit being made by many of these programs have not been substantiated nor have they been reviewed by experts in the field or any regulatory agency. These programs are usually characterized by:
   - Exorbitant fees
   - Misrepresentation of risks and benefits

- Overreliance on, and advertisement of, patient testimony
- Poor patient follow-up
- Absence of regulatory oversight and objective clinical evidence for claimed benefits

Therefore, they differ substantially from therapies approved by legitimate regulatory agencies, from well-designed, controlled, and appropriately regulated clinical trials, and from regulated compassionate use of innovative cell therapies**.** Because of the potential for harm and the lack of any proven benefit, we strongly caution patients not to participate in these or any other comparable unauthorized or unapproved stem cell interventions, unless independent credible, reliable, and objective sources of information are available to substantiate the information and claims being made.

To better educate the lung scientific community about the complex issues of stem cell medical tourism, we propose the inclusion of relevant sessions, whenever possible, in future national and international conferences related to lung biology and disease. Representatives of regulatory agencies, patient advocacy groups, and bioethics and health policy scholars should be included as speakers and discussants. We also urge patient advocacy groups and foundations to work together with their national lung, respiratory, and thoracic societies, their local chapters, and with regulatory agencies on the issues of stem cell medical tourism and unproven stem cell interventions. Open channels of communication between these organizations and dissemination of reliable, evidence-based information through patient networks including social media, will ensure that lung disease patients make informed and safe decisions regarding cell-based treatments. (*Accessed January 2022*)

COPD Foundation

(2015) The COPD foundation has issued the following position related to stem cell therapy for the treatment of COPD:

- Autologous stem cell therapy is not currently recommended for the treatment of COPD. The COPD Foundation does not recommend the use of autologous stem cell therapy in the treatment of COPD or other lung disease until there is more rigorous scientific and medical proof of its effectiveness. Instead, participation in clinical trials that test the development and potential benefit of this technique is strongly encouraged. (*Accessed January 2022*)

Pulmonary Hypertension Association (PHA)

(2009) The Pulmonary Hypertension Association (PHA) issued the following statement:

- Stem cell use has not been adequately studied and neither the efficacy nor safety of stem cells to treat pulmonary arterial hypertension (PAH) has been established. At this time, the Scientific Leadership Council (SLC) recommends stem cell therapy only as part of a registered, clinical trial in carefully selected patients. We

recommend that patients discuss stem cell therapy (and any new therapies) with their PH specialist. (*Accessed January 2022*)

Regulatory Status
The only stem cell-based products that are FDA-approved for use in the United States consist of blood-forming stem cells (hematopoietic progenitor cells) derived from cord blood. These products are approved for limited use in patients with disorders that affect the body system that is involved in the production of blood (called the "hematopoietic" system).

In August 2017, the FDA announced increased enforcement of regulations and oversight of stem cell clinics. The FDA will continue to help with the development and licensing of new stem cell therapies where the scientific evidence supports the product's safety and effectiveness.

In June 2019, the FDA issued a statement regarding their ongoing efforts to protect patients from stem cell clinics who mislead patients with unapproved and harmful medical products. This statement included the following: Stem cell products hold significant potential to improve human health. However, that potential will never be fully realized if careful scientific work and thoughtful clinical investigation supporting the safety and efficacy of these products are not conducted. The FDA is committed to helping advance the safe and effective development of novel stem cell products. We look forward to working with those who share our goal of bringing safe and effective products to market to benefit individuals in need.

PRIOR APPROVAL

Prior approval is recommended.

POLICY

The use of stem cell products including mesenchymal stem cells (MSC) therapy from bone marrow, adipose tissue or peripheral blood, alone or in combination with platelet-derived products (e.g., platelet-rich plasma, lysate) is considered **investigational** for the treatment of lung disease, including but not limited to the following:

- Acute respiratory distress syndrome (ARDS)
- Bronchopulmonary dysplasia (BDP)
- Chronic obstructive pulmonary disease (COPD)
- Idiopathic pulmonary fibrosis (IPF)
- Pulmonary hypertension

Based on the review of the peer reviewed medical literature the use of mesenchymal stem cells (MSCs) from bone marrow, adipose tissue (fat), peripheral blood or other various sites, alone or in combination with platelet-derived products (e.g., platelet-rich plasma, lysate) has not been adequately studied and neither the efficacy nor safety of this stem

cell therapy to treat lung diseases has been established. Further randomized controlled clinical trials are needed to include larger sample sizes with longer follow-up to establish the safety and efficacy of mesenchymal stem cell (MSC) therapy for the treatment of lung disease. Also, the only stem cell-based products that are FDA-approved for use in the United States consist of blood-forming stem cells (hematopoietic progenitor cells) derived from cord blood. Currently the American Lung Association (ALA), the American Thoracic Society, the Pulmonary Hypertension Association and the COPD Foundation do not recommend the use of unproven stem cell therapies at this time for the treatment of lung disease as these groups believe there is not enough known about stem therapies to use them in lung disease without more research. The evidence is insufficient to determine the effects of this technology on net health outcomes.

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 38205 blood derived hematopoietic progenitor cell harvesting for transplantation, per collection allogeneic
- 38206 blood derived hematopoietic progenitor cell harvesting for transplantation, autologous
- 38212 transplant preparation of hematopoietic progenitor cells; red blood cell removal
- 38215 transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear or buffy coat layer
- 38230 bone marrow harvesting for transplantation allogeneic
- 38232 bone marrow harvesting for transplantation autologous
- 38240 Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
- 38241 Hematopoietic progenitor cell (HPC); autologous transplantation
- 0232T injection(s), platelet-rich plasma, any tissue, including image guidance, harvesting and preparation when performed

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POLICY HISTORY

Date	Reason	Action
January 2022	Annual Review	Policy Renewed
January 2021	Annual Review	Policy Revised
January 2020	Annual Review	Policy Renewed
January 2019		New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

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