Review Article

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Stem cell therapy for chronic obstructive pulmonary disease

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Abstract

Chronic obstructive pulmonary disease (COPD), characterized by persistent and not fully reversible airflow restrictions, is currently one of the most widespread chronic lung diseases in the world. The most common symptoms of COPD are cough, expectoration, and exertional dyspnea. Although various strategies have been developed during the last few decades, current medical treatment for COPD only focuses on the relief of symptoms, and the reversal of lung function deterioration and improvement in patient's quality of life are very limited. Consequently, development of novel effective therapeutic strategies for COPD is urgently needed. Stem cells were known to differentiate into a variety of cell types and used to regenerate lung parenchyma and airway structures. Stem cell therapy is a promising therapeutic strategy that has the potential to restore the lung function and improve the quality of life in patients with COPD. This review summarizes the current state of knowledge regarding the clinical research on the treatment of COPD with mesenchymal stem cells (MSCs) and aims to update the understanding of the role of MSCs in COPD treatment, which may be helpful for developing effective therapeutic strategies in clinical settings.

Keywords: Chronic obstructive pulmonary disease; Mesenchymal stem cells; Clinical trial; Inflammation

Introduction

Chronic obstructive pulmonary disease (COPD) is a common respiratory disease that is characterized by persistent respiratory symptoms and airflow limitation. The airway or alveolar abnormalities are usually caused by significant exposure to noxious particles or gases.[1,2] COPD represents an important public health challenge that is preventable and treatable, but there are still many people who die prematurely from it. COPD is currently the fourth leading cause of death in the world and is projected to be the third leading cause of death by 2020.[3,4] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines and classifies COPD based on the severity of airflow obstruction. First, the patients are featured by forced expiratory volume in the first second (FEV_1)/forced vital capacity (FVC) <0.70 and the airflow limitation is not fully reversible.[5] Then, according to the percentage of FEV_1 in the estimated value, COPD was classified into four stages. If FEV_1 is ≥80% of the predicted value, the stage is defined as mild; if FEV_1 is ≥50% and <80% of the predicted value, the stage is defined as moderate; if FEV_1 is ≥30% and <50% of the predicted value, the stage is defined as severe; if FEV_1 is <30% of the predicted value, the stage is defined as very severe.[6]

The pathogenesis of COPD was extremely complicated, which mainly includes airway inflammation, alveolar structure destruction, and excessive expansion mediated by a variety of causes.[7] In general, cigarette smoke and other inhaled particles stimulate the epithelial cells to produce reactive oxygen species, which may induce inflammatory cells, including lymphocytes, neutrophils, macrophages, and eosinophils,[8] to infiltrate around the airway and cause the imbalance of protease/antiprotease.[9] Given that elastin is the main component of connective tissue in the lung parenchyma,[10] the imbalance between protease and antiprotease will further cause lung overinflation, expansion, and loss in lung elasticity, thus resulting in emphysema.[11,12]

Currently, the therapeutic strategies in clinical setting for COPD are relieving symptoms, reducing the frequency and

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severity of exacerbations, and improving exercise tolerance. Although the standard pharmacological therapies, including bronchodilators, inhaled corticosteroids and the phosphodiesterase 4 inhibitor, roflumilast, showed modest efficacy in improving pulmonary function,[13] to date, no conclusive clinical evidence was found to show that any existing medications for COPD could modify the long-term decline in pulmonary function as well as the mortality. Therefore, the development of novel effective treatments to reverse the decline in pulmonary function and reduce the clinical symptoms of the COPD patients is urgently needed.

Stem cells are a class of cells with the ability to self-renew repeatedly, and produce at least one type of highly differentiated progeny.[14,15] The most important function of stem cells is to maintain cell regeneration. Stem cells exist in most tissues of the body from early embryogenesis all the way throughout adult life and are thought to contribute to tissue maintenance and repair.[16] In particular, stem cells could give rise to subsequent generations with variable degrees of differentiation capacities, which offers significant potential for the generation of tissue that could potentially replace diseased and damaged areas in the human body.[17,18] According to different differentiation potential, stem cells can be divided into totipotent stem cells, pluripotent stem cells, and unipotent stem cells.[19] Totipotent stem cells are a kind of cells that have the ability to self-renew and differentiate into any cell types. They have the potential to differentiate into any of the components of a complete individual, such as embryonic stem cells (ESCs).[20] Pluripotent stem cells have the ability to differentiate into many types of cells of a specific organ system, without the ability to develop into complete individual. Unipotent stem cells are unidirectionally differentiated stem cells in many tissues that normally produce only one type of cell.[21] Currently, pluripotent stem cells are most widely used in clinical research due to their broadly acting anti-inflammatory and regenerative properties,[22,23] such as hematopoietic stem cells, mesenchymal stem cells (MSCs), and human lung stem cells (hLSCs).[24] Among them, MSCs are the most widely studied. MSCs exist in a variety of tissues, such as bone marrow, adipose tissue, and umbilical cords. According to the different sources, they are respectively named as bone marrow-derived MSCs (BM-MSCs), adipose-derived MSCs (AD-MSCs), and umbilical cords-derived MSCs (UC-MSCs).[25]

Theoretical Basis

At present, stem cells therapies have been applied to numerous diseases like cardiovascular and cerebrovascular diseases, endocrine system diseases, autoimmune system diseases, malignant tumors, hematopoietic system diseases, neurological diseases, and medical cosmetology industry.[26-29] Of course, many latest findings of stem cells research have also provided new insights into the potential of stem cells to treat a variety of lung diseases, and the stem cell therapy for COPD has gradually become a hot spot.

In recent years, the therapeutic effect of stem cells in animal models of COPD has been demonstrated by many preclinical studies, which mainly focus on BM-MSCs, AD-MSCs, and UC-MSCs.[17,30] People treat the experimental animals with different sources of stem cells, different methods, doses, and times of administration. Stem cell therapy might exert its effects through the following mechanisms: First, stem cell therapy can shorten the mean linear interception, reduce the apoptosis of epithelial cells in the lungs and improve the structure of the damaged lung tissue.[31,32] Second, stem cell therapy can promote the proliferation of a variety of cells in the lung and facilitate the self-repair of lung tissue.[33,34] Third, stem cell therapy can improve pulmonary function to some extent.[35,36] Fourth, stem cell therapy can reduce systemic inflammatory response and promote the secretion of a variety of anti-inflammatory mediators.[37]

Meanwhile, the mechanism of stem cells in the regulation of COPD has been extensively studied.[38] First of all, stem cells are cells with multidirectional differentiation potential. Studies have shown that MSCs can differentiate into type I and/or type II alveolar epithelial cells and participate in the repair of lung tissue structure.[39] In addition to promoting lung structural repair by differentiating into alveolar epithelial cells, stem cell transplantation also inhibits the apoptosis of alveolar epithelial cells.[40,41] Specially, cytokines secreted by MSCs interfere the expression level of apoptotic gene *Bax*, cleaved-caspase 3, and the antiapoptotic gene *Bcl-2* in alveolar epithelial cells.[42,43] It is noted that COPD is the result of an abnormal and persistent inflammatory process that damages the lung architecture.[44] Especially, cigarette smoke activates macrophages, neutrophils, and lymphocytes in the lung, causing the release of a variety of inflammatory cytokines that result in COPD progression.[45,46] MSCs have shown the ability to slow the progression of COPD by effectively decreasing the inflammatory response with attenuated classic activated macrophage cytokine release including interleukin (IL)-1β, IL-6, tumor necrosis factor alpha and monocyte chemotactic protein 1 and promoting the release of anti-inflammatory mediators, like IL-10, transforming growth factor-β, indoleamine 2,3 dioxygenase 1.[18,35] Another equally important factor for the pathogenesis of COPD is the balance of proteases and antiproteases. The imbalance of protease/antiprotease will cause the degradation of extracellular matrix,[47] promote the apoptosis of alveolar wall structure cells, increase the high secretion of mucus and finally lead to the destruction of alveolar wall and the expansion of air space.[48] Previous data have shown that stem cells reversed the up-regulation of matrix metalloproteinases induced by cigarette smoke.[49] Indeed, MSCs can effectively inhibit the progression of COPD by regulating the balance between proteases and antiproteases.[50] Additionally, stem cell transplants can also reduce oxidative stress in the lung tissue.[51] Excessive oxidative stress will cause cell damage and further aggravate the inflammatory response in the lung by inducing the release of inflammatory cytokines.[52]

Clinical Research

On the basis of the previous preclinical research, the results of clinical trials for stem cells are also being gradually integrated. This paper provides an overview of clinical

trials in the treatment of COPD with stem cells, which is crucial for researchers to get clearer understanding of the current research situation and achieve the ultimate goal of curing patients with COPD.

MSCs are pluripotent stem cells that share all the characteristics of stem cells: self-renewal, immunomodulatory, and multipolarity.[53,54] MSCs were first described in the bone marrow where they constitute a small fraction of cells (0.001%–0.01%) that closely interact with hematopoietic cells to support hematopoiesis and skeletal homeostasis.[14] Since then, it has become evident that MSCs reside in many tissues, including mesenchymal tissues (bone, adipose tissue, connective tissue), umbilical cord, and several organs including the liver, spleen, and lung.[55-57] There are no specific markers for MSCs, therefore, they are identified by their expression of a range of markers and their functional characteristics. Nowadays in most clinical trials, the MSCs were derived from bone marrow.

Bone marrow-derived stem cells

The first clinical trial of cell therapy in COPD patients was an uncontrolled phase I clinical trial (ClinicalTrials.gov identifier: NCT01110252) carried out in Brazil from May 2009 to October 2009.[58,59] The purpose of this study was to evaluate the safety of bone marrow-derived monocytes (BM-MCs) infusion procedure in patients with advanced COPD (GOLD stage IV). With a single intravenous infusion, each patient received a total of 1×10^8 cells. Unlike other subsequent studies using BM-MSCs, the cells used in this study were BM-MCs, which were isolated directly from bone marrow without subsequent *in vitro* culture. The 12-month follow-up after the BM-MCs infusion showed that there were no adverse reactions. Therefore, the researchers claimed that this treatment was quite safe. The laboratory analysis reported a slight improvement in pulmonary function in all patients, chiefly in the first 30 days after the procedure was carried out. In addition, the results showed that their clinical conditions also improved to some extent. However, because of the small size (only four patients) and lack of statistical analysis in this design, the results did not support definite conclusions.[59] It should be noted that this study was the first clinical trial of cell therapy in COPD patients, and it provided meaningful guidance for the clinical cell therapy of COPD in the future.

Five years after the first clinical trial using BM-MCs to treat COPD, a prospective, randomized, double-blind, placebo-controlled trial (ClinicalTrials.gov identifier: NCT00683722) of BM-MSCs in COPD was conducted by Weiss *et al*[60] in the United States. The goals of this study were to evaluate safety and efficacy of MSCs treatment and the effect of MSCs on circulating inflammatory mediators. In this study, 62 patients with moderate to severe COPD (GOLD stage II or III) were randomized to double-blinded infusions of either allogeneic MSCs or vehicle control. Patients received four monthly infusions (1×10^8 cells/infusion) and were subsequently followed for 2 years after the first infusion. There were several significant improvements in this clinical trial, compared to the first one. First, the number of enrolled cases increased significantly, from 4 to 62. Second, the input cells were improved from BM-MCs to BM-MSCs. After *in vitro* culture, the BM-MSCs, which were isolated from BM-MCs through further screening of growth mode, would have better proliferation capacity. Third, the authors made a change in the frequency of administration, increased from a single dose to four, monthly. Fourthly, the source of the cells was also changed, from autogenous to allogeneic. The researchers in this clinical trial found that allogeneic MSCs administration seemed also safe in patients with moderate to severe COPD. They did not observe some infusion related toxicities and serious clinically relevant adverse events. No statistically significant differences were observed in pulmonary function and quality of life. There were also no significant differences in the frequency of COPD exacerbations or worsening of disease in this study. It was exciting to observe a significant decrease in C-reactive protein (CRP) levels up to 1 month after the first infusion with MSCs in patients who had elevated CRP levels at study entry, indicating that the systemic inflammatory response in these patients was reduced by MSCs to some extent. Although no significant improvements in clinical symptoms and pulmonary function were observed in this study, sufficient cases provide more confidence about the safety of MSCs in the treatment of COPD.

In another study, Stolk *et al*[61] finished a phase I, prospective open-label trial (ClinicalTrials.gov identifier: NCT01306513) to observe the safety and feasibility of BM-MSCs intravenous administration. They selected ten patients with severe COPD who would undergo lung volume reduction surgery (LVRS). The BM-MSCs therapy was performed 8 weeks after the first LVRS, with $(1–2) \times 10^6$ cells/kg BM-MSCs injected intravenously once a week for 2 weeks. A second LVRS was performed one month after the stem cell treatment. Finally, the study showed that there were no serious adverse events observed and the lung tissue showed no fibrotic responses. FEV_1 and body weight increased in all patients but showed no difference between two groups. Considering that these patients all had experienced LVRS, the changes in FEV_1 and body weight were more likely to be resulted from LVRS than from BM-MSCs infusion.[62] The current study would only demonstrate that LVRS itself had a substantial effect on FEV_1, but would not be further enhanced by the BM-MSCs treatment.[63] The most prominent feature of this clinical trial was that the patients included were about to undergo LVRS, thus, the researchers were able to obtain lung tissue before and after the stem cell treatment. Through the comparative study of lung histopathological sections before and after BM-MSCs treatment, the researchers can more intuitively understand the effect of stem cells on lung tissue at the pathological and microscopic levels. Thus, for safety evaluation, this study not only focused on the occurrence of adverse events, but also intuitively demonstrated that BM-MSCs treatment would not cause any adverse changes in lung structure. Surprisingly, after BM-MSCs infusion, alveolar septa showed a three-fold increased expression of the endothelial marker CD31, which suggested that BM-MSCs therapy might promote endothelial repair. In addition, the dosage

of BM-MSCs was also adjusted. Instead of fixing the total number of the cells, the researchers gave the patients different amounts of cells depending on their body weight.

The above three clinical trials all transplanted MSCs into patients via intravenous infusion. However, whether the stem cells would circulate throughout the body or migrate directly to damaged lung tissue is unknown. Armitage *et al*[64] conducted a single site, phase I clinical trial (Australian clinical trials identifier: 12614000731695) to observe the distribution of stem cells *in vivo* and the systemic inflammatory response after intravenous infusion. Nine patients received two infusions of allogeneic BM-MSCs of 2×10^6 cells/kg once a week for 2 weeks. BM-MSCs used for the first infusion were labeled with indium-111 to monitor its location in the body. The results showed that BM-MSCs infusion had no attributable adverse effects and was well tolerated. BM-MSCs were detected in the lung within 30 min and remained detectable after 24 h, after which, BM-MSCs were mainly distributed in the liver. After the injection of BM-MSCs, the number of hospitalized patients with acute exacerbations of COPD decreased, but there was no significant improvement in pulmonary function. However, BM-MSCs tended to migrate to normal lung tissue rather than emphysema areas, which may be a reason why stem cell therapy has no significant effect on pulmonary function. Many inflammatory mediators, such as F2-isoprostanes, IL-6, and CD163, showed a decreasing trend 1 to 7 days after treatment. It is worth noting that CRP exhibited a transient elevated state 1 to 2 days after stem cell intervention, which contrasts with data from another clinical trial where systemic administration of allogeneic BM-MSCs in COPD patients reduced CRP levels 1 to 3 months after infusion.[65]

Considering that the stem cells, which were injected intravenously, did not stay in the lung long enough to exert its role, researchers began to try new ways of administration. Compared with intravenous administration, intratracheal administration is a more direct and accurate mode of drug application. A phase I, prospective, patient-blinded, randomized, placebo-controlled study (ClinicalTrials.gov identifier: NCT01872624), which was implemented by de Oliveira *et al*,[65] attempted to treat COPD by intratracheal administration of BM-MSCs combined with one-way endobronchial valves (EBV) insertion for the first time. In this trial, ten patients (GOLD stage III or IV) were divided into two groups, randomly receiving either allogeneic BM-MSCs (1×10^8 cells) or 0.9% saline solution bronchoscopically, just before insertion of one-way EBVs. In the EBV + MSCs group, no patient experienced adverse events and the serum CRP levels were significantly reduced in 30 and 90 days compared to EBV + saline group. No statistically significant between-group differences in pulmonary function indicators were observed. EBV + MSCs group had a significant lower body mass index, airflow obstruction, dyspnea, and exercise capacity index, lower modified medical research council (mMRC) scores, and decreased Saint George's respiratory questionnaire (SGRQ) scores. Consistent with above data, in this study, intrabronchial administration of MSCs in severe COPD patients was relatively safe and was able to reduce systemic inflammation by reducing the level of CRP and to improve life quality of COPD patients.

All in all, above clinical trials indicated that administration of allogeneic or autologous BM-MSCs is safe and no adverse side-effects are observed. Additionally, the therapeutic effects of BM-MSCs need more clinical trials to confirm.

Adipose tissue-derived stem cells

Adipose tissue is another major source of MSCs. Compared to bone marrow, adipose tissue contains a much higher percent of MSCs.[66,67] In addition, AD-MSCs have higher proliferative capability,[68] retain differentiation potential for a longer period and have increased immunomodulating capacity compared to BM-MSCs.[69] Adipose stromal cells 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).[70] The SVF, which is easy to obtain, contains all cellular elements of fat excluding adipocytes and can be used as an option for stem cell therapy.[71]

A non-randomized, phase I, open label trial (ClinicalTrials.gov identifier: NCT02041000) was performed by Comella *et al*.[72] Twelve patients with COPD participated in the clinical trial. The researchers isolated SVF from the patients' adipose tissue and infused $(1.5–3) \times 10^8$ cells back to the patients intravenously. The primary purposes of this study were to evaluate the feasibility and safety of SVF infusion in COPD patients. During the infusion and 12 months of follow-up, no adverse events were observed. Unlike other studies, this trial focused specifically on patients' subjective feelings such as the attitudes towards the procedure and the willingness to undergo next procedure of stem cells treatment. Attitudes toward the study were predominantly positive, three stated that there was no effect, 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. Surprisingly, the SGRQ score was decreased from 73 units at baseline to 45 at 3 months ($P = 0.005$) and to 44 at 6 months ($P = 0.008$) after treatment. The clinical trial relied on subjective patient feedback, but lacked objective clinical evidence such as pulmonary function tests. Therefore, infusion of autologous SVF was safe and might improve the quality of life for patients with COPD, but it was necessary to determine whether it has a positive impact on pulmonary function within further studies.

Umbilical cord-derived stem cells

UC-MSCs have been reported as promising MSCs sources for treating various diseases in humans, including heart failure,[73,74] ankylosing spondylitis,[75] type 2 diabetes mellitus,[76] and angioplasty for diabetic feet.[77] BM-MSCs are most commonly used in clinical trials of stem cell therapies. However, with the development of stem cell research, the shortage of BM-MSCs is gradually exposed. Human BM-MSCs from aged patients would highly

express senescence-related genes, have shorter telomere length, low proliferation, and low differentiation capacity.[78] This will inevitably lead to obstacles in the treatment of autologous stem cell transplantation. Through comparative analysis, the researchers found that UC-MSCs exhibit strong modulation capacity. In addition, under the same conditions, UC-MSCs inhibited allogeneic lymphocytes more strongly than BM-MSCs and AD-MSCs did.[79] UC-MSCs also had higher proliferation rates and exhibited better potential to differentiate into other cells due to its better primitiveness.[80] Therefore, when allogeneic stem cell transplantation is needed (such as in elderly patients), UC-MSCs is a better choice.

Le Thi Bich *et al*[81] finished a pilot clinical trial (ISRCTN70443938) of treating COPD with UC-MSCs. In this study, 20 patients with COPD at stage C or D (GOLD) were enrolled. UC-MSCs were isolated from umbilical cord samples of donors during childbirth. All patients were intravenously infused with expanded allogeneic UC-MSCs (1.5×10^6 cells/kg) and followed for 6 months after the first infusion. Interestingly, no serious or clinically significant adverse events were observed for all patients during the study. Unfortunately, the pulmonary function showed no statistically significant differences before and after the treatment of UC-MSCs. It was satisfactory to find that the mMRC score, COPD assessment test score, and number of exacerbations decreased significantly after 1, 3, and 6 months compared with those before treatment, which suggested that UC-MSCs can improve the patient's quality of life. And there was an interesting phenomenon that stage D COPD patients exhibited a stronger medical response after UC-MSCs transplantation than stage C COPD patients did, which was in contrast to another study, in which researchers found COPD patients with mild disease retained MSCs in the pulmonary vasculature longer than those with more severe disease did.[64] Perhaps this difference can be attributed to the use of different sources of MSCs, but further research is really needed. The trial was the first clinical trial to use MSCs from umbilical cord tissue to treat COPD patients. Conclusions can be drawn that UC-MSCs administration appears to be safe in patients with moderate-to-severe COPD and can significantly improve their quality of life.

In the latest research, Karaoz *et al*[30] finished an open-label, single-armed study carried out in LIV hospital in Istanbul. After the pre-treatment measurements, all the patients were administered a total of four doses of UC-MSCs ($1–2 \times 10^6$ cells/kg) by intravenous infusion at 2-week intervals. Respiratory function tests, SGRQ scores, and 6 min walk test were next examined. Surprisingly, UC-MSCs therapy not only improved patients' quality of life but also improved pulmonary function to some extent. The mean pre-treatment FEV_1/FVC ratios were only 66.90% while the mean FEV_1/FVC value raised to 69.58% after the treatment. The greatest difference between this clinical trial and the clinical trial conducted by Le Thi Bich *et al*[81] is the schedule of administration. Single dose was adopted by Le Thi Bich *et al*,[81] while Karaoz *et al*[30] increased the number of doses to double, with an interval of 2 weeks, which is likely to be one of the reasons for the difference in the result of pulmonary function. Certainly, the shortcomings of this clinical trial exist, such as the small number of cases (only five) and the short follow-up time (only 3 months). However, it still offered a glimmer of hope for future stem cell treatment of COPD.

hLSCs

hLSCs refer to the cells that can differentiate into functional lung tissues under specific conditions and play an important role in maintaining lung tissue renewal and repairing lung injury.[82] They can be isolated from lung tissue and have similar cell surface markers with other stem cells. The difficulty of obtaining human lung tissue significantly limited the study of this type of cells. Nevertheless, lung stem cells (LSCs) may be involved in alveolar homeostasis and post-injury repair and may need to be considered as a potential tool or target when referring to stem cell therapy. In animal experiments, the effect of LSCs has been confirmed. Injecting LSCs into the airway of emphysema model mice can effectively reduce the severity of emphysema and improve the survival of mice.[83,84] However, it is difficult to transform the animal experiments into clinical practice because of the difficulty to obtain human lung tissue. Moreover, rejective reaction of host-*vs*.-graft is still a troubling aspect needed to consider after the LSCs injection therapy. Although it is impossible to directly treat COPD with exogenous LSCs infusion, it is possible to activate endogenous LSCs with specific drugs. For example, studies have shown that all-trans-retinoic acid (ATAR) may activate the endogenous stem/progenitor cells in the lung that result in lung structural regeneration.[85]

Summary

In the above eight clinical trials (the trial of ATAR was not included in the discussion), the researchers used different kinds of stem cells, different cell sources, different modes, and dosages of administration to treat COPD. There are both similarities and differences in the final results. In the following part, we will analyze the possible improvement methods of stem cell treatment for COPD by comparing the differences in each trial design and the different results [Table 1].

Cell types

In the current clinical trials of stem cell therapy for COPD, the main cell types used were MSCs because other kind of stem cells all have their own limitations. ESCs have potentials for forming teratoma and immune rejection, and there are ethical concerns for application of ESCs; induced pluripotent stem (iPS) cells can form teratoma, and the current technique cannot produce reliable amount of clinical-grade iPS cells[86,87]; LSCs are also a good research direction, but clinical trials are not easy to carry out because of the difficulty in obtaining lung tissue. The most common sources of MSCs are bone marrow, fat and umbilical cord, which are respectively named as BM-MSCs, AD-MSCs, and UC-MSCs. Some studies pointed out that BM-MSCs have decreased differentiation potential and maybe suboptimal for this line of therapy.[88] At

Table 1: Clinical trials on the stem cell therapy for COPD with published results.

	Basic information				Experimental scheme					Main results			
PMID	Registry code	Patients (*n*)	Cell/drug type	Cell source	Mode of administration	Schedule of administration	Dosage of administration	Other special treatment	Follow-up period	Safety	Pulmonary function	Symptoms and quality of life	Other important results
21311694	NCT01110252	4	BM-MCs	Autologous	i.v.	Single dose	1×10^8	Granulocyte colony-stimulating factor	1 year	No related adverse events occur	FEV_1, FEV_1%, FVC, FVC% improved temporarily after 1 month of treatment	A greater time tolerance without O_2 intake by nasal catheter; a greater capacity on exertion without significant fall in saturation	–
23172272	NCT00683722	62	BM-MSCs	Allogeneic	i.v.	Four times, interval of 1 month	1×10^8	–	2 years	No significant differences in the overall number of adverse events, frequency of COPD exacerbations, or worsening of disease	No significant differences in FEV_1%, FVC%, and FEV_1/FVC	No significant differences in 6MWT, SGRQ, and Borg dyspnea scale	CRP level decreased at 1 month
26819296	NCT01306513	10	BM-MSCs	Autologous	i.v.	Twice, interval of 1 week	$(1–2) \times 10^6$/kg	Lung volume reduction surgery	1 year	No related adverse events occur; lung tissue sections showed no fibrotic responses	FEV_1 improved, but had no significant difference compared with the control group	Weight improved, but had no significant difference compared with the control group	CD31 expression in lung tissue increased
29348155	Australian clinical trials: 12614000731695	9	BM-MSCs	Allogeneic	i.v.	Twice, interval of 1 week	2×10^6/kg	–	1 year	No related adverse events occur	No significant differences in FEV_1% and FVC%	There was a reduction in hospital admissions for acute exacerbations of COPD	MSCs was detected in the lung within 30 min and remained detectable after 24 h; MSCs tended to migrate to normal lung tissue rather than emphysema areas; inflammatory response indicators decreased
28186686	NCT01872624	10	BM-MSCs	Autologous	i.t.	Single dose	1×10^8	One-way EBV insertion	3 months	No significant between-group differences were observed in overall number of adverse events	No significant differences in FEV_1%, FVC%, RV%, TLC%, DLCO%	BODE and mMRC scores decreased	CRP level decreased at 30 and 90 days
28725319	NCT02041000	12	AD-SVF	Autologous	i.v.	Single dose	$(1.5–3) \times 10^8$	–	1 year	No related pulmonary or cardiac adverse events occur	-	92% of the study subjects expressed a desire to undergo the procedure a second time	Three stated that the treatment had no effect, 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
32054512	ISRCTN70443938	20	UC-MSCs	Allogeneic	i.v.	Single dose	1.5×10^6/kg	–	6 months			mMRC scores, CAT scores, and the	Stage D COPD patients exhibited a

(*continued*)

Table 1
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PMID	Basic information				Experimental scheme					Main results			
	Registry code	Patients (*n*)	Cell/drug type	Cell source	Mode of administration	Schedule of administration	Dosage of administration	Other special treatment	Follow-up period	Safety	Pulmonary function	Symptoms and quality of life	Other important results
32115975	–	5	UC-MSCs	Allogeneic	i.v.	Twice, interval of 2 weeks	$(1–2)\times10^6$/kg	–	3 months	No related severe adverse events occur	The mean FEV_1/FVC ratios were raised	SGRQ scores decreased and the mean walking distance of 6MWT extended	–
11874821	–	20	ATAR	–	Orally	12 weeks, twice a day for 4 days/week	25 $mg·m^{-2}·d^{-1}$	–	6 months	Well tolerated and associated with only mild side effects	No significant differences in FEV and FEV_1/FVC%	No significant differences in QOL questionnaires	No overall difference in the extent of emphysema was observed by CT

AD-SVF: Adipose-derived stromal vascular fraction; ATRA: All-trans-retinoic acid; BM-MCs: Bone marrow-derived mesenchymal cells; BM-MSCs: Bone marrow-derived mesenchymal stem cells; BODE: Body mass index, airflow obstruction, dyspnea, and exercise capacity index; CAT: COPD Assessment Test; COPD: Chronic obstructive pulmonary disease; CRP: C-reactive protein; CT: Computed tomography; DLCO: Diffusing capacity of carbon monoxide; EBV: Endobronchial valves; FEV_1: Forced expiratory volume in the first second; FVC: Forced vital capacity; i.v.: Intravenous injection; i.t.: Intratracheal injection; mMRC: Modified Medical Research Council; MSC: Mesenchymal stem cells; QOL: Quality of life; RV: Residual volume; SGRQ: Saint George's respiratory questionnaire; TLC: Total lung capacity; UC-MSCs: Umbilical cord-derived mesenchymal stem cells; 6MWT: 6 min walk test.

the same time, many studies have shown that AD-MSCs and UC-MSCs are very promising cells because the source is quite available. In addition, the process of collecting UC-MSCs is non-invasive, and there has been no tumorigenicity reported up to date.[18,89] Trends in clinical trials are also consistent with this conclusion, the early clinical trials were mainly focused on BM-MSCs, while in recent years, the clinical trials related to AD-MSCs and UC-MSCs gradually increased. Until there is a better choice, AD-MSCs and UC-MSCs may be the mainstream research targets for the treatment of COPD with stem cells.

Cell sources

The source of cells is either from autologous or allogeneic. In the early days, people were afraid to use allogeneic stem cells for clinical trials mainly for fear of immune transplant rejection. However, it has been proved that the safety of allogeneic MSCs transplanted into COPD patients is good, and there are no related adverse reactions.[60,64,81] On the premise of good safety, we can further compare the advantages and disadvantages of autologous stem cells and allogeneic stem cells. For UC-MSCs, it is not practical to choose cells from autogenous source, so cells from allogeneic source would be the only choice. For BM-MSCs and AD-MSCs, we can use either MSCs from autogenous or allogeneic. Studies have shown that human BM-MSCs from aged patients would highly express senescence-related genes, with shorter telomere length, low proliferation, and low differentiation capacity.[90] In addition, the patients will suffer a certain degree of pain in the process of bone marrow or fat acquisition. Some adverse reactions related to puncture and liposuction may occur at the same time. Therefore, for elderly patients, allogeneic stem cells may be a better choice. However, allogeneic stem cells also have their own problems. The biggest one is in the storage of the cells, because liquid nitrogen cryopreservation will cause a decrease in cell activity, and they cannot play the maximum therapeutic effect.[91] Whether to use autologous or allogeneic stem cells will be up to the researchers to make a judgment based on the actual situation.

Mode, schedule, and dosage of administration

The research showed that after the stem cells were injected into the body intravenously, they concentrate in the lungs for the first half hour and then gradually migrate to the liver.[64] The inability of stem cells to stay in the lung for longer time may affect the therapeutic effects of stem cells. There are two ways to solve this problem, that is by adjusting the schedule of administration or mode of administration. By comparing the two UC-MSCs trials, we found that multiple doses may have a better therapeutic effect than single dose.[30,81] Therefore, increasing the number of doses is an ideal improvement for future stem cell research. In addition, airway injection by bronchoscope is a good way to transfer the stem cells directly to the patient's lungs. Of the eight completed clinical trials, there was only one trial which directly transplanted stem cells into patients via airway injections. Although the result of this experiment was negative, it is one of the directions of our future development. In terms of the dosage of

Table 2: Clinical trials registered at ClinicalTrials.gov on stem cell therapy for COPD.

Registry code	Trial status	Patient (*n*)	Cell/drug type	Cell source	Mode of administration	Schedule of administration	Dosage of administration	Other special treatment	Primary outcome measures	Follow-up period
NCT02348060	Recruiting	100	AD-SVF	Autologous	i.v.	Single dose	–	–	Quality of life	1 year
NCT04047810	Recruiting	15	MSCs	–	i.v.	Single dose	$(0.5–2) \times 10^6$/kg	–	Number of adverse events	1 year
NCT03040674	Recruiting	200	BM-MCs	Autologous	i.v.	Single dose	–	–	Quality of life and FEV_1	1 year
NCT03909750	Recruiting	50	AD-SVF	Autologous	i.v.	Single dose	–	–	Safety and pulmonary function	6 months
NCT02946658	Recruiting	100	AD-SVF	Autologous	i.v.	Single dose	–	–	Safety and pulmonary function	1 year
NCT04206007	Active, not recruiting	9	UC-MSCs	Allogeneic	i.v.	Single dose	–	–	Number of adverse events	1 year
NCT04018729	Not yet recruiting	34	BM-MSCs	Autologous	i.t.	Single dose	–	Endobronchial valve	Number of adverse events and quality of life	6 months
NCT02216630	Completed	26	AD-SVF	Autologous	i.v.	Single dose	–	–	FEV_1 and number of adverse events	1 year
NCT02645305	Completed	20	AD-SVF	Autologous	i.v.	Single dose	–	Platelet rich plasma	Blood SGOT levels	1 year
NCT01758055	Unknown	12	BM-MSCs	Unknown	i.v.	Single dose	0.6×10^8	–	Pulmonary function	1 year
NCT02135380	Unknown	60	AD-SVF	Autologous	i.v.	3 times, once a week	2×10^6/kg	–	Safety	1 year
NCT03044431	Unknown	214	BM-MCs	Autologous	i.v.	Single dose	–	Platelet rich plasma	FEV_1 and quality of life	6 months
NCT02412332	Unknown	20	BM-MSCs/ AD-MSCs	Autologous	i.v.	Single dose	1×10^8	–	Pulmonary function	1 year
NCT01849159	Withdrawn	-	BM-MSCs	Allogeneic	i.v.	6 times, once 2 months	–	–	Safety	2 years
NCT03228121	Withdrawn	-	BM-MCs	Autologous	i.v.	3 times, once a day	–	Platelet rich plasma	Quality of life and FEV_1	1 year
NCT01559051	Terminated	-	AD-SVF	Autologous	i.v.	Single dose	–	–	Number of adverse events and 6-min walk test	6 months
NCT02161744	Terminated	9	AD-SVF	Autologous	i.v.	Single dose	–	–	Safety	1 year

AD-MSCs: Adipose-derived mesenchymal stem cells; AD-SVF: Adipose-derived stromal vascular fraction; BM-MCs: Bone marrow-derived mesenchymal cells; BM-MSCs: Bone marrow-derived mesenchymal stem cells; CAT: COPD assessment test; COPD: Chronic pulmonary obstructive disease; FEV_1: Forced expiratory volume in the first second; i.v.: Intravenous injection; i.t.: Intratracheal injection; MSCs: Mesenchymal stem cells; SGOT: Serum glutamic-oxaloacetic transaminase; UC-MSCs: Umbilical cord-derived mesenchymal stem cells.

administration, the eight clinical trials have maintained a high level of consistency, basically at (1–3) $\times 10^8$ cells or (1–2) $\times 10^6$ cells/kg. Most researchers are conservative in this aspect because the schedule of administration can be adjusted, and too many cells per dose may cause unintended consequences.

Experimental results

No matter what type of MSCs, which would be transplanted into the lungs of COPD patients, in what mode of administration, it has been proved to be safe. There were no adverse events associated with stem cell transplantation. In terms of the effect of stem cells on pulmonary function, only 2 clinical trials reported that MSCs could improve pulmonary function (autologous BM-MCs 1×10^8 and allogeneic UC-MSCs [1–2] $\times 10^6$/kg), and the remaining six clinical trials all showed that MSCs had no effect on it. In view of the small number of patients (4 and 5, respectively) enrolled in the two clinical trials that showed a therapeutic effect of stem cells on pulmonary function, further research is needed to see whether MSCs can improve it. In eight clinical trials, six studies suggested that MSCs transplantation could improve patients' quality of life, while the other two studies on BM-MSCs showed no effect on it. We believe that stem cell transplantation may have the ability to improve patients' quality of life, perhaps because of the placebo effect, the inhibition of systemic inflammatory response or other extra-cognitive effects. In addition, stem cell transplantation would disrupt the CRP level, which rises briefly 1 to 2 days after transplantation, followed by persistent low expression for several months.

At present, 17 clinical trials on the treatment of COPD with stem cells are registered at ClinicalTrials.gov. The relevant information is summarized in Table 2. In future clinical trials, the following suggestions may be effective in improving the experimental design: (1) expand the sample size; (2) extend the follow-up time to 2 years or even longer; (3) select patients with different grades of COPD to determine the most suitable subjects for MSCs treatment; (4) AD-MSCs and UC-MSCs are more inclined to be used in future research compared with BM-MSCs; (5) multiple injections to enhance the treatment effect; (6) teams with appropriate clinical conditions may attempt to perform MSCs transplantation through bronchoscope; (7) assess lung function and quality of life comprehensively to obtain more accurate research data; (8) further explore the effects of MSCs on changes in other inflammatory, immune, and metabolic indicators. It is believed that stem cell therapy may play a revolutionary role in the treatment of COPD and other respiratory diseases in the near future.

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Conflicts of interest

None.

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