Clinical applications of mesenchymal stem cells in chronic lung diseases (Review)

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Abstract. Mesenchymal stem (stromal) cells (MSCs) are multipotent stromal cells that have the ability to modulate immune response to tissue injury and promote repair *in vivo*. The therapeutic potential of *ex vivo* expanded MSCs are currently under investigation for a variety of chronic and acute lung diseases. This review summarizes the encouraging results regarding the safety of MSCs administration from recent and current clinical trials for idiopathic pulmonary fibrosis, acute respiratory distress syndrome, and chronic obstructive pulmonary disease. It also reviews the early preliminary data extracted by the same trials regarding the efficacy of MSCs in the aforementioned lung diseases.

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1. Introduction

Mesenchymal stem (stromal) cells (MSCs) are multipotent stromal cells that can be isolated from bone marrow (BM), skeletal muscle, amniotic fluid and adipose tissue, among other tissues with a differentiation potential towards adipocytes, chondrocytes, and osteoblasts. Embryonic stem cells (ESCs) and adult stem cells are the two main categories of stem cells in human (1). Previous data suggested that stem cells may participate in tissue homeostasis and regeneration after injury and may originate either from the lung itself, termed resident progenitor cells (alveolar, endothelial and interstitial), or from distant sites such as blood, BM and adipose tissue, namely endothelial progenitor cells (EPCs) and MSCs, as previously mentioned (2-6). Adult-derived stem cells, such as MSCs have the ability to modulate immune response to tissue injury and promote repair *in vivo*, and have been suggested as an attractive therapeutic candidate for a variety of lung diseases, including idiopathic pulmonary fibrosis (IPF), acute respiratory distress syndrome (ARDS), and chronic obstructive pulmonary disease (COPD) (7). The main objective of this review is to highlight the main clinical studies of MSCs in humans regarding the application of stem cell as a novel treatment option in chronic lung diseases, including IPF, ARDS and COPD.

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2. Mesenchymal stem cells

MSCs are multipotent cells characterized by their ability to differentiate into varying cell lines and to exert anti-proliferative, immunomodulatory, and anti-inflammatory effects. Recent studies have focused on the potential therapeutic applications of stem cells based on their multipotency, migratory ability, and immunoprivileged properties. MSCs have been extensively studied as a treatment option in various diseases, including severe graft versus host disease, pancreatic islet and renal glomerular repair in diabetes, ischemic acute renal failure, acute lung injury, and as cardiac function restorers after acute cardiac ischemic events (7-12).

Concerning the lungs, data from animal models have already shown the contribution of MSCs to tissue regeneration after elastase-induced emphysema, home to sites of asbestos-induced lung injury, and restoration of alveolar and lung fluid balance after endotoxin-induced acute lung injury (13,14). Thus, the therapeutic potential of *ex vivo* expanded MSC is of great interest.

Table I. Clinical trials of MSCs in respiratory diseases.

Study (year)	Disease/ Condition	Cell Type	Delivery Route	Primary Endpoint	Refs.
Ribeiro-Paes *et al* (2011)	Advanced COPD	BMMC	IV	Safety of SC infusion	(36)
Weiss *et al* (2013)	Moderate to severe COPD	BM-MSCs	IV	Safety of systemic MSC administration	
Tzouvelekis *et al* (2013)	Mild to moderate IPF	ADSCs-SVF	EB	Safety (incidence of treatment emergent adverse events)	(19)
Zheng *et al* (2014)	ARDS	AD-MSCs	IV	Safety (possible adverse events after systemic administration of AD-MSCs)	(29)
Chambers *et al* (2014)	Moderate IPF	PD-MSCs	IV	Safety and feasibility of an infusion of PD-MSCs	(20)
Wilson *et al* (2015)	Moderate to severe ARDS	BM-MSCs	IV	Safety of BM MSCs intravenous infusion	(28)
Baughman *et al* (2015)	Advanced Pulmonary Sarcoidosis	PD-MCs	IV	Acute effect of cell therapy on pulmonary artery pressure	(37)
Stolk *et al* (2016)	Severe emphysema	BM-MSCs	IV	Safety and feasibility of IV administration of BM-MScs	(33)
Glassberg *et al* (2017)	Mild to moderate IPF	BM-MSCs	IV	Safety of a single infusion of BM-MSCs	(21)

BMMC, bone marrow mononuclear cells; IV, intravenously; SC, stem cell; BM-MSCs, bone marrow derived mesenchymal stem cells; ADSCs-SVF, adipose derived stem cells-stromal vascular factor; Endobronchially; AD-MSCs, adipose derived-mesenchymal stem cells; PD-MSCs, placenta derived-mesenchymal stem cells; PD-MCs, placenta derived-mesenchymal-like cells.

Tropea *et al* suggested that exposure to exogenous stem cells may induce the proliferation of resident endogenous progenitor cells in the lungs, thus contributing to tissue repair in a murine model (15). Moreover, bronchioloalveolar stem cells are capable of resisting bronchiolar and alveolar damage and proliferating during epithelial cell renewal (16). Jarvinen *et al* have shown anti-inflammatory and immunomodulatory properties of lung resident progenitor cells (17). Finally, Kajstura *et al* recently described a human lung resident stem cell line with the capacity for differentiation into bronchioles, alveoli, and pulmonary vasculature (5).

Despite all the aforementioned reports, a limited number of trials have been recorded in humans, owing to safety risks together with a limited knowledge of the mechanism of action of the various stem cell therapies that inevitably hinders the choice of optimal cell therapy.

3. MSCs and IPF

IPF is a lung disease of unknown origin characterized by loss of lung epithelial cells, parenchymal tissue remodeling, distortion of lung architecture, respiratory insufficiency and poor outcome despite the introduction of two novel therapeutic agents, pirfenidone and nintedanib (18). The pathogenesis of IPF is characterized by epithelial cell injury, interstitial inflammation, extracellular matrix collagen deposition, and eventual loss of function. MSCs are home to sites of injury, inhibit inflammation, and contribute to epithelial tissue repair. Thus, their use has been suggested as a potential therapy for the treatment of IPF (19).

A recent single center, open-label phase 1b study by Tzouvelekis *et al* assessed the safety profile of the endobronchial administration of adipose derived stromal cells-stromal vascular fraction (ADSCs-SVF; n=14), in patients with mild to moderate IPF. Stability in functional and exercise tolerance was found in the majority of the studied population (86%) 1 year after follow-up. There were no reported serious or clinically relevant side effects in the 24-month follow-up period after the first infusion (20) (Table I).

In another recent single center phase 1 study, by Chambers *et al* patients with IPF received intravenous placenta-derived hMSCs (n=8). In this non-randomized, dose escalation phase 1b trial, patients with moderately severe IPF [diffusing capacity for carbon monoxide (DLCO) ≥25% and forced vital capacity (FVC) ≥50%] received either $1x10^6$ (n=4) or $2x10^6$ (n=4) unrelated-donor, placenta-derived MSC/kg via a peripheral vein and were followed for 6 months with lung function (FVC and DLCO), 6-min walk distance (6MWD) and chest computed tomography. Most adverse events (AEs) were mild and self-limiting and no deaths were reported (21) (Table I).

Recent results from the AETHER study, published by Glassberg *et al* (22), constituted the first human trial designed to evaluate the safety of BM-derived human allogeneic MSCs (BM-hMSCs) in patients with mild to moderate IPF. In this non-randomised, non-placebo single-centre clinical trial, BM-MSCs from two men were cultured and subsequently administered as a single intravenous infusion to nine patients with mild to moderate IPF. No treatment -related serious AEs were reported with infusions up to $2x10^8$ cells over a 60-week follow-up period. Two non-study related deaths were recorded. Non-serious AEs unrelated to treatment were reported in most patients (78%), most frequently bronchitis and the common cold. Mean absolute declines of 3.0% predicted FVC and

5.4% predicted DLCO were described 60 weeks after infusion, which are below the internationally accepted thresholds representing disease progression (22) (Table I).

4. MSCS and ARDS

ARDS is characterized by acute hypoxemic respiratory failure that develops primarily from an increase in lung endothelial and epithelial permeability. ARDS develops in response to multiple predisposing factors, including pneumonia, systemic sepsis, as well as major surgery or multiple trauma, with pulmonary and extrapulmonary sepsis accounting for 75% of all predisposing causes of ARDS. The pathologic hallmark of ARDS consists of diffuse alveolar damage, with injury to both the lung endothelium and epithelium (23,24).

Preclinical data support the therapeutic potential of several stem cell types for ARDS. ESCs have been differentiated to produce functional airway epithelium, while MSCs derived from ESCs attenuate murine endotoxin- and bleomycin-induced lung injury (25,26). Regarding EPCs, which comprise circulating progenitor cells involved in the repair of endothelial cells, data from several preclinical studies have shown encouraging results in cases of endotoxin lung injury (27,28).

Recently, a phase 1b dose escalation study, was published by Wilson *et al*, with three doses of human BM-MSCs (1, 5, and 106 MSCs/kg ideal body weight) given intravenously over 1 h in 9 patients with moderate to severe ARDS [defined as a PaO_2/FiO_2 <200 mmHg ventilated with at least 8 cmH_2O positive end-expiratory pressure (NCT01775774)] (29). This research group is now conducting a randomized, blinded phase 2a safety trial in 60 patients [40 treated with MSCs at 106 MSCs/kg ideal body weight and 20 with plasmalyte placebo (NCT02097641)] (Table I).

Zheng *et al* assessed the safety profile of MSCs with the administration of a low dose of 1 million adipose-derived hMSCs/kg in 12 adult patients meeting the Berlin definition of ARDS. 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. No infusion toxicities or serious AEs related to MSCs administration were reported, although the clinical effect was weak (30) (Table I).

5. MSCs and COPD

COPD is the fourth leading cause of death worldwide and a major cause of chronic morbidity and mortality. Experimental models have aimed to investigate the pathophysiology of pulmonary emphysema as one of the main expressions of COPD and to identify new treatment approaches, as the current treatment aims are supportive and not curative. Nevertheless, the first animal model of rodent MSC administration in COPD has been published (31,32).

Weiss *et al* reported a phase II, multicenter, randomized, double-blind placebo-controlled study, to evaluate the safety and efficacy of intravenous allogeneic MSCs for the treatment of moderate to severe COPD (33). Thirty COPD patients received four monthly infusions of MSCs (100x106 cells/infusion) with a 2-year follow-up. The primary endpoint was safety, assessed by occurrence of AEs, electrocardiography (ECG), and COPD exacerbations. The results demonstrated that the administration of MSCs in patients with moderate to severe COPD appears to be safe, with no AEs or an increased rate of exacerbations recorded during the study. However, no significant clinical improvement was detected.

Currently, the only treatment available for severe emphysema is lung volume reduction surgery (LVRS). Stolk *et al* reported a phase I, non-randomized, non-blinded, prospective study, regarding the safety and feasibility of administering BM-MSCs before and after LVRS for severe emphysema (34). Two BM-MSCs infusions in 10 patients 1 week apart, 4 and 3 weeks prior to the second LVRS, respectively were performed. No AEs related to the infusions were observed in the first 48 h and at 3 weeks after the second infusion, or the day before the second LVRS.

Furthermore, a phase I, non-randomized, open-label study has recently been completed, regarding the safety evaluation of MSC administration in patients with severe heterogeneous emphysema and placement of one-way endobronchial valve (35). In addition, that study investigated whether this treatment modality modulates other markers of inflammatory response and remodeling. Five patients received BM-MSC immediately preceding insertion of one-way endobronchial valves by bronchoscopy. No AEs or lung deficits during the procedure and/or follow-up were reported.

Currently, several clinical trials are ongoing worldwide regarding the safety and efficacy of stem cell based therapies in COPD including ASDC, BM-MSC, and plerixa for mobilization of CD117 stem cells to peripheral blood. The current cell dosage has not elicited a long-term therapeutic effect. Further evaluation of efficacy and safety of systemic and local administration of autologous or allogeneic MSCs in the treatment of COPD is needed.

6. Conclusion

In conclusion, recent clinical trials of autologous or allogeneic MSCs administration in patients with various respiratory diseases provide adequate evidence for the safety of use of MSCs in those groups of patients. Consequently, phase II human trials including different sources, doses and routes of administration are the next step in the assessment of the efficacy of MSCs in respiratory diseases.

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Competing interests

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