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Cell therapy for lung disease

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Cell-based therapies for lung diseases are evolving to become viable treatment options for clinical application <http://ow.ly/oXe130crWmw>**Cite this article as:** Geiger S, Hirsch D, Hermann FG. Cell therapy for lung disease. *Eur Respir Rev* 2017; 26: 170044 [<https://doi.org/10.1183/16000617.0044-2017>].

ABSTRACT Besides cancer and cardiovascular diseases, lung disorders are a leading cause of morbidity and death worldwide. For many disease conditions no effective and curative treatment options are available. Cell therapies offer a novel therapeutic approach due to their inherent anti-inflammatory and anti-fibrotic properties. Mesenchymal stem/stromal cells (MSC) are the most studied cell product. Numerous preclinical studies demonstrate an improvement of disease-associated parameters after MSC administration in several lung disorders, including chronic obstructive pulmonary disease, acute respiratory distress syndrome and idiopathic pulmonary fibrosis. Furthermore, results from clinical studies using MSCs for the treatment of various lung diseases indicate that MSC treatment in these patients is safe. In this review we summarise the results of preclinical and clinical studies that indicate that MSCs are a promising therapeutic approach for the treatment of lung diseases. Nevertheless, further investigations are required.

Introduction

The human lung has a surface area of 35–100 m² (inflation status-dependent) allowing efficient exchange of oxygen required for oxidative metabolism [1]. This contact area is exposed to airborne toxins and micro-organisms and their products. Despite these constant insults, in healthy individuals the lung is able to regulate immune reactions (upregulation and down-modulation of responses) and to control tissue plasticity needed for repair after injury, allowing the maintenance of homeostasis [2]. Although the aetiologies of various lung diseases are still unclear, their complex pathology is in many cases associated with dysregulation in immune responses (e.g. chronic inflammation in chronic pulmonary disease) and aberrant repair processes of lung tissue (e.g. idiopathic pulmonary fibrosis (IPF)).

As cell therapies represent multimodal therapeutic agents with the ability to influence immune and regenerative functions [3–6], they are an attractive treatment option for lung diseases. This review focuses on mesenchymal stem/stromal cells (MSCs). MSCs have been shown to possess anti-inflammatory and anti-fibrotic properties due to the secretion of various cytokines and soluble factors, which affect a variety of immune cells and promote tissue regeneration [7–9]. This review summarises data from preclinical and clinical trials which demonstrate that MSCs are effective and safe for the treatment of lung diseases (table 1).

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a heterogeneous continuum of diseases with a high morbidity and mortality and was the fourth leading cause of death worldwide in 2015 [34]. It is

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TABLE 1 Some recent preclinical and clinical studies of lung diseases using mesenchymal stem/stromal cells (MSCs)

Indication	Study	Cell source	Dose	Application route	Study design	Result	Reference
COPD	Preclinical	Human MSCs, bone marrow-derived	0.1, 5, 25 or 125×10^3 MSCs·g ⁻¹	<i>i.v.</i>	Elastase-induced emphysema in mice	Reduced fibrosis, reduced inflammation	[10]
COPD	Preclinical	Human MSCs, cord blood-derived	5×10^4 MSCs per mouse	<i>i.v.</i>	Cigarette smoke-induced COPD in mice	Reduced inflammation, increased regeneration	[11]
COPD	Preclinical	Rat MSCs	6×10^6 MSCs per rat	<i>i.t.</i>	Cigarette smoke-induced COPD in rats	Reduced inflammation, improved lung function	[12]
COPD	Preclinical	Rat MSCs, bone marrow-derived	6×10^6 MSCs per rat	<i>i.t.</i>	Cigarette smoke-induced COPD in rats	Reduced inflammation	[13]
COPD	Preclinical	Human MSCs, bone marrow or iPSC-derived	3×10^6 bone marrow-derived MSCs or iPSC-derived MSCs per mouse	<i>i.v.</i>	Cigarette smoke-induced COPD in mice	Reduced inflammation	[14]
COPD	Clinical	Allogeneic human MSCs, bone marrow-derived, non-HLA-matched	4-monthly infusions of 100×10^6 MSCs per patient	<i>i.v.</i>	Phase 2, prospective, randomised, double-blind, placebo (vehicle)-controlled (n=62)	MSC treatment was safe, no improvement of lung function, reduced levels of CRP	[15]
Emphysema	Clinical	Allogeneic human MSCs, bone marrow-derived	1×10^8 MSCs per patient	Br.	Phase 1, prospective, patient-blinded, randomised, placebo-controlled (n=10)	MSC treatment was safe, reduced systemic inflammation	[16]
ALI/ARDS	Preclinical	Human MSCs, umbilical cord- and bone marrow-derived	1×10^7 human MSCs·kg ⁻¹	<i>i.v.</i>	<i>Escherichia coli</i> -induced ALI in rats	Prolonged animal survival, reduced inflammation	[17]
ALI/ARDS	Preclinical	Syngeneic murine MSCs	2.5×10^5 MSCs per mouse	<i>i.v.</i>	LPS-induced ALI in mice	Reduced inflammation, reduced lung permeability	[18]
ALI/ARDS	Preclinical	Syngeneic murine MSCs	5×10^5 MSCs per mouse	<i>i.v.</i>	Bleomycin-induced ALI in mice	Prolonged animal survival, reduced inflammation	[19]
ALI/ARDS	Preclinical	Human MSCs	5×10^5 MSCs per mouse	<i>i.t.</i>	LPS-induced ALI in mice	Prolonged animal survival, reduced pulmonary oedema	[20]
ALI/ARDS	Preclinical	Rat MSCs, bone marrow-derived	5×10^6 MSCs per rat	<i>i.v.</i>	LPS-induced ALI in rats	Reduced inflammation, reduced lung permeability	[21]
ALI/ARDS	Preclinical	Rat MSCs, bone marrow-derived	5×10^6 MSCs per rat	<i>i.v.</i>	LPS-induced ALI in rats	Reduced inflammation, reduced lung injury	[22]
ALI/ARDS	Preclinical	Human MSCs, menstrual blood-derived	1×10^6 cells per mouse	<i>i.v.</i>	LPS-induced ALI in mice	Reduced inflammation, reduced lung permeability, reduced lung injury	[23]

Continued

TABLE 1 Continued

Indication	Study	Cell source	Dose	Application route	Study design	Result	Reference
ALI/ARDS	Clinical	Allogeneic human MSCs, bone marrow-derived	1×10^6 , 5×10^6 or 10×10^6 MSCs·kg ⁻¹	<i>i.v.</i>	Phase 1, multicentre, open-label, dose-escalation study (n=9)	MSC treatment was safe Improvement of mean lung injury score and SOFA score Decrease in levels of IL-6 and IL-8	[24]
ALI/ARDS	Clinical	Allogeneic human MSCs, adipose tissue-derived	1×10^6 MSCs·kg ⁻¹	<i>i.v.</i>	Phase 1, randomised, placebo-controlled pilot study (n=12)	MSC treatment was safe	[25]
IPF	Preclinical	Allogeneic murine MSCs, bone marrow-derived	5×10^4 MSCs·g ⁻¹	<i>i.v.</i>	Bleomycin-induced fibrosis in mice	Reduced fibrosis	[26]
IPF	Preclinical	Allogeneic murine MSCs, bone marrow-derived	5×10^5 MSCs per mouse	<i>i.v.</i>	Bleomycin-induced fibrosis in mice	Reduced inflammation	[27]
IPF	Preclinical	Human MSCs, Wharton's jelly-derived	1×10^6 MSCs per mouse	<i>i.v.</i>	Bleomycin-induced fibrosis in mice	Reduced inflammation	[28]
IPF	Preclinical	Human MSCs, adipose-derived	40×10^6 MSCs·kg ⁻¹	<i>i.v.</i>	Bleomycin-induced fibrosis in mice	Reduced fibrosis	[29]
IPF	Preclinical	Syngeneic MSCs, bone marrow-derived	5×10^5 MSCs per mouse	<i>i.t.</i>	Bleomycin-induced fibrosis in mice	Improved pulmonary respiratory functions, reduced fibrosis	[30]
IPF	Preclinical	Autologous rat MSCs, bone marrow-derived	2×10^6 MSCs per rat	<i>i.v.</i>	Silica instillation-induced fibrosis in rats	Reduced fibrosis	[31]
IPF	Clinical	Allogeneic human MSCs, placenta-derived	1×10^6 or 2×10^6 MSCs·kg ⁻¹	<i>i.v.</i>	Phase 1b, single-centre, nonrandomised, dose escalation study (n=8)	MSC treatment was safe No evidence of worsening fibrosis	[32]
IPF	Clinical	Autologous adipose tissue-derived MSCs	5×10^5 MSC·kg ⁻¹	<i>i.v.</i>	Phase 1b, prospective, nonrandomised, not placebo-controlled (n=14)	MSC treatment was safe	[33]

COPD: chronic obstructive pulmonary disease; ALI: acute lung injury; ARDS: acute respiratory distress syndrome; IPF: idiopathic pulmonary fibrosis; *i.t.*: intratracheal; iPSC: induced pluripotent stem cells; HLA: human leukocyte antigen; CRP: C-reactive protein; Br.: bronchoscopy; LPS: lipopolysaccharide; SOFA: sequential organ failure assessment; IL: interleukin.

characterised by chronic inflammation in the lung parenchyma as a response to inhaled noxious particles, emphysema, fibrosis and mucus hypersecretion, resulting in progressive expiratory airflow obstruction [35]. Only symptomatic treatment is available for COPD [36].

MSC-based products have been studied extensively in animal models of COPD due to their tissue-regenerative and immunomodulatory properties.

Human bone marrow-derived (bm)MSCs reduced fibrosis as analysed by histological scoring of lung sections using the Ashcroft scale; apoptosis as measured by a reduction of DNA strand breaks; and inflammation as seen by a reduction of interleukin (IL)-1 β , IL-6 and tumour necrosis factor (TNF)- α levels in an elastase-induced mouse model of COPD [10]. Interestingly, findings from our own laboratory indicate that the efficacy of bmMSCs in this model can be improved further if the cells are genetically modified to express the potent protease inhibitor α_1 -antitrypsin [37, 38] (S. Geiger, unpublished data).

In addition, in cigarette smoke-induced models of COPD, human and rat MSCs induced a regeneration mechanism in the lung as indicated by changes in expression profiles of genes responsible for immune responses, metabolic processes and blood vessel development [11]; ameliorated emphysema and pulmonary function as demonstrated by statistically higher forced expiratory volume in 100 ms/forced vital capacity (FVC) [12]; and decreased inflammation, possibly through the inhibition of cyclooxygenase-2/prostaglandin E2 in alveolar macrophages [13]. A recent study found that human induced pluripotent stem cell-derived MSCs were more effective than bmMSCs in ameliorating cigarette smoke-induced inflammation in rats by reducing neutrophil and macrophage infiltration [14]. Although these results are very encouraging, the translatability of preclinical animal models of COPD to the human situation is somewhat limited, since COPD is a very complex and heterogeneous disease, and all of the known animal models are only able to mimic some aspects of the disease (as reviewed in [39]).

Based on the promising preclinical data, MSCs are currently being investigated for the treatment of COPD in several clinical trials. WEISS *et al.* [15] included 62 patients in a randomised double-blinded phase I study of COPD. Treatment with non-human leukocyte antigen-matched allogeneic MSCs appears to be safe in COPD patients. Notably, while there was no significant difference in pulmonary function as measured by forced expiratory volume in 1 s, FVC and total lung capacity, the 6-min walk test, oxygen saturation, number of exacerbations, quality-of-life (QoL) parameters and circulating C-reactive protein (CRP) levels were significantly decreased in patients, suggesting that MSCs can inhibit the inflammation present in COPD [15]. The same decrease in CRP levels was observed in a phase I, prospective, patient-blinded, randomised, placebo-controlled study in which 10 patients suffering from advanced emphysema were treated with allogeneic bmMSCs [16]. Furthermore, MSC treatment improved COPD predictors such as the body mass index, airway obstruction, dyspnoea, exercise capacity (BODE) index and QoL parameters in this trial, prompting the need for further studies assessing the potential of MSCs for the treatment of COPD.

Acute respiratory distress syndrome

The acute respiratory distress syndrome (ARDS), a clinical complication of acute lung injury (ALI), is a devastating condition characterised by a dysfunction of the lung epithelial barrier and the capillary endothelium, diffuse alveolar damage and interstitial oedema, leading to rapidly progressive acute respiratory failure [40–43]. ARDS can be caused by various clinical disorders, most commonly bacterial or viral pneumonia, sepsis, major trauma or aspiration [41]. ARDS mortality rates remain as high as 20–40% [24], thus, novel therapeutic approaches are needed. MSCs have proven to be efficacious in various animal models. CURLEY *et al.* [17] demonstrated that treatment of rats with human umbilical cord (uc)MSCs in a model of *Escherichia coli*-induced ARDS resulted in a reduction of disease severity as determined by prolonged survival, improved oxygenation and a decrease in inflammatory parameters such as a reduced alveolar infiltration of neutrophils, decreased bronchoalveolar lavage (BAL) levels of IL-6 and TNF- α and increased levels of the anti-inflammatory proteins IL-10 and TNF-stimulated gene 6 protein. The same significant amelioration of pulmonary inflammation, reflected by reductions in neutrophil counts in BAL fluid and reduced levels of proinflammatory cytokines was observed using syngeneic MSCs in a murine model of lipopolysaccharide (LPS)-induced ARDS [18]. Interestingly, administration of MSCs genetically modified to express the vasculoprotective protein angiopoietin-1 additionally resulted in nearly complete reversal of LPS-induced increases in lung permeability in the same study. SAITO *et al.* [19] reported that the anti-inflammatory activity of MSCs can be improved by the expression of the C-C motif chemokine ligand 2 inhibitor 7ND. 7ND-MSCs have a significantly enhanced activity in a bleomycin-induced murine ARDS model, compared to native MSCs.

Recently, the resolution of ALI achieved by MSCs in mouse models is partially mediated through the lipid mediator lipoxin A₄, as seen by reduced levels of macrophage inflammatory protein (MIP)-2 and TNF- α in the BAL fluid [20]. Furthermore, lipoxin A₄ enhances the phagocytic activity of alveolar macrophages [44], thereby restoring alveolar fluid clearance and decreasing inflammation [45]. Additionally, two paracrine factors are essential for the beneficial effects of MSC treatment in preclinical models of ALI/ARDS: YANG *et al.* [21] and HU *et al.* [22] found that vascular endothelial growth factor and hepatocyte growth factor expression from MSCs is crucial for the protection of pulmonary vascular permeability as measured by Evans blue dye extravasation and for the prevention of endothelial cell apoptosis, as well as the reduction of proinflammatory IL-1 β levels and the increase in anti-inflammatory IL-10 levels in lung tissue in rat models of ALI/ARDS. Even MSCs derived from fairly uncommon sources such as menstrual blood (menSCs) have recently proven to be efficacious in a murine model of ALI/ARDS [23]. Treatment with menSCs led to attenuated inflammation, as determined by reduced levels of IL-1 β and increased levels of IL-10 in the BAL fluid and plasma, and to repair of the damaged lung tissue as seen by increased proliferating cell nuclear antigen expression as a marker for proliferation and a decrease in the apoptotic marker caspase 3.

MSC treatment for ARDS is currently being tested in several clinical trials, so far demonstrating an excellent safety profile. WILSON *et al.* [24] performed a multicentre, open-label phase I dose escalation clinical study to test the safety of a single dose of *i.v.* allogeneic bmMSCs for the treatment of moderate-to-severe ARDS. Nine patients were assigned to three dose groups and injected with a single dose of 1, 5, and 10 million MSCs·kg⁻¹ bodyweight (bw). No prespecified infusion-associated adverse events were recorded. Ventilator-free days for each patient were 24, 0 and 18 days in the low-dose group; 22, 0 and 27 days in the intermediate-dose group; and 26, 12 and 20 days in the high-dose group. The mean lung injury score, as well as the sequential organ failure assessment score which quantifies the severity of organ dysfunction improved in a cell dose-dependent manner in all three dose groups, and there was a decrease in levels of IL-6 and IL-8. However, none of these results reached statistical significance, and a matched control group was missing in this study. Currently, a randomised, double-blind placebo-controlled phase II clinical trial of 10 million MSCs·kg⁻¹ bw in 60 patients with moderate-to-severe ARDS is being conducted by the same group. The results generated in the aforementioned study overall recapitulate the results achieved in a previous phase I trial assessing the therapeutic effect of a single dose (1 million MSCs·kg⁻¹ bw) of allogeneic adipose tissue-derived (a)MSCs for the treatment of ARDS in 12 patients [25]. The favourable tolerability and short-term safety profile that MSC treatment with doses as high as 10 million cells·kg⁻¹ bw exhibited in both of these clinical trials strongly suggests that MSC treatment is safe, and that further studies are warranted to assess beneficial effects of MSC treatment in ARDS.

Idiopathic pulmonary fibrosis

IPF is a progressive, irreversible lung disease associated with accumulation of fibroblasts in the parenchyma that results in characteristic fibrotic scar formation and with alterations in lung tissue architecture characterised by destroyed lung tissue containing numerous cystic airspaces with thick fibrous walls, referred to as honeycombing. In most cases, the disease trigger is unknown, but a link to impaired wound healing after recurrent epithelial injuries is assumed [26]. Due to limited treatment options, the prognosis is often poor with a median survival time of ~3 years after diagnosis [30]. Therefore, novel therapies are under investigation.

The bleomycin-induced fibrosis model is the most common preclinical *in vivo* model used to evaluate a potential therapeutic effect of MSCs on fibrotic lung diseases [26]. In this model, early administration of bmMSCs or ucMSCs during the initial inflammatory phase resulted in a protective effect: reduced levels of proinflammatory cytokines, decreased deposition of activated fibroblasts and collagen and improved epithelial repair. However, no therapeutic or profibrotic effects were observed when treated in the subsequent fibrotic phase [26–28]. Compared to the treatment with the anti-fibrotic and anti-inflammatory drug pirfenidone, *i.v.* injection of human aMSCs was more effective in ameliorating bleomycin-induced lung fibrosis [29]. Further improvement of the protective effects of MSCs on pulmonary function, inflammation and fibrosis were observed with hypoxic pretreatment of MSCs by increased secretion of anti-inflammatory, anti-apoptotic and anti-fibrotic factors upon hypoxic treatment [30]. Additionally, genetic modification of MSCs to express bone morphogenetic protein-7 has been shown to improve the protective effects of MSC therapy [31]. Although the murine bleomycin-induced model is the best-characterised model for IPF, with similarities to human IPF pathogenesis, it does not cover all aspects of the human disease, particularly regarding disease progression. Therefore, the translatability of preclinical data to clinical efficacy is limited [46].

Several phase I clinical studies assess MSCs for the treatment of IPF. Since IPF patient-derived MSCs express reduced levels of tissue protective growth factors, allogeneic MSCs should be favoured [47]. CHAMBERS *et al.* [32] performed a phase I clinical study to assess the feasibility and safety of *i.v.*-injected placenta-derived MSCs for the treatment of IPF. Patients were treated with 1×10⁶ or 2×10⁶ MSCs·kg⁻¹ bw. Lung function was monitored for 6 months. Only minor adverse events were reported, but there was no evidence of worsening fibrosis. Hence, MSC treatment was considered to be safe. These data are in line with a previous study addressing the safety of aMSCs. Patients received three endobronchial infusions (0.5×10⁶ MSC·kg⁻¹ bw per infusion). No indication of serious adverse events or deterioration of lung function was observed [33].

Conclusion

There is a growing body of evidence that MSC-based therapies for lung diseases are evolving to become viable treatment options for clinical application. In particular, the potential of genetically engineered MSCs, which allows for considerable enhancement of the therapeutic activity, warrants further investigation. Several aspects of cell-based therapies still need further elucidation: the route of administration (intratracheal or systemic), the exact dose regimen and the need for repeated treatment, as well as the use of allogeneic or autologous MSCs and the optimal source of MSCs.

Cell-based therapies are costly treatments. In our opinion, the best chance of clinical and commercial success for cell-based therapies is in life-threatening (acute) diseases. Therefore, development strategies should focus on off-the-shelf products that may be generated from allogeneic donor material.

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