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Research Article

Trends and Outlook for Stem Cell Therapy in Lung Damage Patients

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Abstract

Stem cell therapy is regenerative medicinal therapy used to repair damaged cells by lowering inflammation and controlling the immune system. Stem cells differentiate into cell types requested for repair. Cell therapy is useful for treating chaotic, hysterical pulmonary sickness.

The stem cell treatment has been found safe and well tolerable.

Currently, most of the stem cell trials are at an early stage for assessing the worth of safety, practicability, tolerance, and productiveness. Stem cell therapy on respiratory diseases needs to be studied by phase III and IV clinical trials. Mesenchymal stromal cell (MSC)-Stem cell based therapies provide a platform for new therapeutic strategies in lung diseases. Cell-based therapies are costly treatments.

The global stem cell therapy market size was estimated at USD 11.22 billion in 2022 and it is projected to reach around USD 31.41 billion by 2030. Approximately 87.5% of our total patient population reported sustained improvement in their condition within three months of treatment.

Keywords: *Pulmonary Diseases; COVID-19; Cell Therapy; Mesenchymal Stem Cells (MSCs); Bronchopulmonary Dysplasia (BPD); Pulmonary Fibrosis*

Introduction

Respiratory diseases are a top-ranked cause of death toll worldwide [1].

Acute and chronic lung diseases, including COVID-19, acute lung injury acute respiratory distress syndrome, bronchopulmonary, sarcoidosis, and chronic obstructive pulmonary diseases [2].

Idiopathic pulmonary fibrosis, have high morbidity and mortality [3].

Cell-based therapy may be a promising therapeutic strategy for lung injury repair [4].

Mesenchyme stromal stem cells derived from the umbilical cord blood, bone marrow, placenta, are tested by registered clinical trials [5].

Stem cells are able to repair injured airways and lungs [6].

Stem cells used for the treatment of pulmonary fibrosis include endogenous, embryonic stem cells, induced pluripotent stem cells [7,8].

MSCs are currently the most commonly used stem cells in clinical trials [9].

Nebulization-based delivery of stem cells therapy have a significant loss of cell viability [10,11].

MSCs are multipotent cells in combination with their low or absent constitutive HLA class I and II expression [12].

MSCs in pulmonary fibrosis produce anti-inflammatory, immunosuppressive, and angiogenic properties [13].

Stem cell discoveries recognized their complex immunomodulatory role [14].

Stem cells have the ability to differentiate into type II alveolar epithelial (ATII) cells [15,16].

The first tissue-engineered trachea, utilizing the patient's own stem cells, has been successfully transplanted into a young woman a case of tuberculosis [17].

When the ESC derivatives were employed in an attempt to repair injured lung tissue *in vivo*, a number of problems emerged [18].

Human bone marrow-derived MSCs reduced fibrosis and inflammation by a reduction of interleukin (IL)-1β, IL-6 in an elastase-induced mouse model of COPD [19].

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 [20].

Types of stem cells

Embryonic stem cells

Isolated from the inner cell mass of blastocysts. In developing embryo, stem cells can differentiate into regenerative organs, such as blood, skin and intestinal tissues.

Adult stem cells

Present in bone marrow, adipose tissue and blood of adults.

Umbilical cord stem cells

Collected during birth and stored in cell banks throughout the life.

Stem cell therapy

The stem cell transplantation is accompanied with chemotherapy:

1. Chemotherapy is used to wipe off the patient's affected blood cells.
2. Followed by injecting new stem cells which will renew the production of new healthy immune cells.

Stem cell therapy in pulmonary diseases

COPD

Chronic obstructive pulmonary disease includes both chronic bronchitis and emphysema.

Currently, there is no cure for chronic obstructive pulmonary disease (COPD) using stem cell therapy. While some studies have shown promising results, more research is needed to determine its long-term efficacy.

Stem cell therapy is still considered a novel treatment for lung diseases and has not yet been accepted into mainstream medicine.

Current treatment for COPD involves the use of anti-inflammatory drugs combined with other therapies. However, current therapies have limited effectiveness. Phuong Le., *et al*. has shown that allogeneic umbilical cord-derived mesenchymal stem cell transplantation is both a safe and effective treatment option for both moderate to severe COPD disease patients [21].

Study Methods

Twenty patients were enrolled in the study; patients were infused with expanded allogeneic umbilical cord tissue derived mesenchyme stem cells (MSCs). All patients were followed for 6 months after the first infusion. The treatment end-point included a comprehensive safety evaluation, pulmonary function testing (PFT), and quality-of-life indicators including questionnaires, the 6-min walk test (6MWT), and systemic inflammation assessments. All patients completed the full infusion and 6-month follow-up.

Results and Discussion

The study concluded that MSC treatment was safe. There were no infusion-related toxicities, deaths, or severe adverse events occurred that were deemed related to UC-MSC administration. The UC-MSC-transplanted patients showed a significantly reduced Modified Medical Research Council score, COPD assessment test, and number of exacerbations. This study showed that allogeneic non-HLA-matched UC-MSC transplantation is a safe treatment that improved the quality of life of COPD patients. This clinical study was the first to use allogeneic MSCs from umbilical cord tissue to treat COPD.

Stem cell-based therapy for pulmonary fibrosis (PF)

The safety and therapeutic efficacy of stem cell transplantation have to be resolved [22].

It was summarized that fibrogenesis in PF, highlighting the roles of stem cells derived from different sources in the repair of fibrotic lung tissues. Then, we analyzed some key concerns that should be considered in the clinical treatment of PF with different types of stem cells, such as the administration route, dose and frequency. In addition, the superiority of and current problems with stem cell-derived exosomes for the treatment of PF were also discussed. To conclude, we speculated that stem cell-based therapy has great promise for PF.

Although studies have shown that MSCs can improve the lung function of patients with PF, they cannot eliminate fibroblasts, degrade unwanted ECM, or regenerate the alveolar epithelium [23,24].

Embryonic stem cells

ESCs are pluripotent stem cells isolated from blastocysts that can be induced to generate a variety of specialized cell types.

Coraux., *et al.* showed that murine ESCs could differentiate into alveolar epithelial cells, when the cells were cultured at the **air**-liquid interface, indicating the potential of transplanting human embryonic stem (hES)-ATII cells as an effective strategy to treat the injured epithelium in airway diseases [25].

Access to information on clinical trials

The U.S. government compiles a list of all registered clinical trials in the U.S. and abroad, including clinical trials for stem cell treatments. This can be easily accessed on the website www.clinicaltrials.gov. You can use keywords such as "stem cells" and your lung disease diagnosis such as "chronic obstructive pulmonary disease", "cystic fibrosis", or "pulmonary fibrosis" to find clinical trials [26].

There is a rapid pace of clinical trials on stem cell therapy for lung diseases in the last 5 years. Because of the heterogeneity of pulmonary diseases, a broad spectrum of stem/progenitor cells has chosen by registered trials. Meanwhile, diverse routes for delivering and doses have applied based on both preclinical and clinical studies. It is a long-lasting debate if MSCs result in aggregating or clumping in the injured microcirculation and carry the risk of mutagenicity and oncogenicity. Few clinical studies have described clinical improvements. Therefore, further optimization for cell therapy on respiratory diseases needs to be explored by more phase III and IV clinical trials. Cell therapy has significant challenges for gene editing stem cells, optimized route and dose, intervention regimes and applications for individual case, nevertheless, cell-therapy offers a most innovative strategy for unmanageable respiratory diseases [27].

Acute respiratory distress syndrome

Current advances in supportive care, morbidity and mortality remain high in patients with acute respiratory distress syndrome (ARDS) [28].

ARDS pathology is driven by an acute severe inflammatory response, and acknowledging that the general hypothesis is that MSCs mainly act as immunomodulatory cells via rapid-acting paracrine effects, ARDS could be an ideal target for MSC-based therapies [29,30].

In 2014, MSC-based treatment entered clinical trials for ARDS patients. In this trial, allogeneic adipose-derived MSCs were administered to 12 ARDS patients [31].

A subsequent phase 1 dose-escalation safety trial using a single dose of allogeneic bone marrow-derived MSCs at 1.0, 5.0, and 10.0×10^6 cells per kg of predicted body weight in 9 ARDS patients was conducted [32].

These two trials were early phase 1 studies with the primary outcome being safety and were both underpowered to detect significant differences in efficacy. Both trials showed that MSCs were well tolerated in ARDS patients.

Using stem cells to treat lung sarcoidosis

Four patients with severe pulmonary sarcoidosis received intravenous infusions of 300 million placenta-derived mesenchymal stem cells. The cells were split into two doses, given one week apart.

Broncho pulmonary dysplasia

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 MSC-based therapies to treat BPD has increased especially in response to findings in pre-clinical studies demonstrating positive benefits [33,34].

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 1×10^7 or 2×10^7 cells per kg [35].

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 [36].

Recent advancements in stem cell technology

It opens a new door for patients suffering from diseases and disorders that have yet to be treated. Stem cell-based therapy, including human pluripotent stem cells (hPSCs) and multipotent mesenchymal stem cells (MSCs), has recently emerged as a key player in regenerative medicine. hPSCs are defined as self-renewable cell types conferring the ability to differentiate into various cellular phenotypes of the human body, including three germ layers.

Stem cells could save lives in lung damage

For the first time, Australian researchers have found a type of stem cell that could prove crucial in reducing injury and scarring in the lung and even generate new lung cells. A recent study has revealed that human cells isolated from the placenta could potentially heal lung injuries in patients. Australian researchers have found a type of stem cell that could prove crucial in reducing injury and scarring in the lung and even generate new lung cells. Lead researcher, associate professor Yuben Moodley, who is now at the Lung Institute of Western Australia, University of Western Australia, and a physician at the Royal Perth Hospital said: "The investigation could provide hope for patients suffering from lung damage".

Researchers discover disease-causing stem cells in lungs of cystic fibrosis patients

Using single cell cloning technology that detailed stem cell heterogeneity in lungs from patients with COPD and idiopathic pulmonary fibrosis (IPF), identified five stem cell variants common to lungs of patients with advanced CF, including three that show hyperinflammatory gene expression profiles and drive neutrophilic inflammation upon xenografting to immunodeficient mice," said Xian, research professor in biology and biochemistry [36].

Current information about stem cell therapy

The use of stem cells for treating lung diseases has great appeal. Sometimes the treatment could cause adverse effects and could worsen the patient's condition.

It is expensive therapy. Because of the possible harm, the lack of any authorized benefit, and the high fees that many of these programs charge, guidelines to conduct pulmonary stem cell therapy.

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 Clinicaltrials.gov. We are hopeful that there will be more in the future.

Under permissible category, Stem cells treatment, strictly has to follow ICMR guidelines for biomedical research and GCP guidelines of Government of India, may be carried out with prior approval of Institutional Committee for Stem Cell Research and Therapy (IC-SCRT), Institutional Ethics Committee (IEC).

Can stem cell therapy cure lung diseases?

Currently, there is no cure for most lung diseases using stem cell therapy. Stem cell therapy is still considered a novel treatment for lung diseases and has not yet been accepted into mainstream medicine.

What is the outlook for stem cell therapy?

Cell-based therapies are costly treatments.

The global stem cell therapy market size was estimated at USD 11.22 billion in 2022 and it is projected to reach around USD 31.41 billion by 2030 and growing at a compound annual growth rate (CAGR) of 13.73% during the forecast period 2023 to 2030.

What is the success rate of stem cell therapy?

Preliminary data from our stem cell clinic and others have shown promise in the effectiveness of stem cell treatments. Approximately 87.5% of our total patient population reported sustained improvement in their condition within three months of treatment.

Conclusion

Cell therapies offer a novel therapeutic approach due to their inherent anti-inflammatory and anti-fibrotic properties. There is a rapid pace of clinical trials on stem cell therapy for lung diseases in the last 5 years. Mesenchyme stem cells (MSCs) are able to modulate proliferation, activation, and effector function of all immune cells that play an important role in the pathogenesis of acute and chronic inflammatory lung diseases. In addition to the suppression of lung-infiltrated immune cells, MSCs have potential to differentiate into alveolar epithelial cells *in vitro* and, accordingly, represent new players in cell-based therapy of inflammatory lung disorders.

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.

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