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CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is an age related heterogeneous and complex lung disease. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines COPD as "a preventable and treatable disease state characterized by airflow limitation that is not fully reversible" (GOLD, 2017). Cigarette smoking is still the most common risk factor. The chronic airflow obstruction characteristic of COPD is a result of chronic lung inflammation and it is characterized by a spectrum of two distinct and commonly overlapping processes: bronchitis (small-airway disease) and emphysema (parenchymal destruction with loss of alveolar units); the relative contributions of each component varies from person to person.

According to the World Health Organization, in 2016 Chronic Obstructive Pulmonary Disease (COPD) became the third leading cause of death in the world and the fifth cause of deaths in high-income countries (https://www.who.int/respiratory/copd/en/). COPD therefore represents an important and increasing public health challenge.

Current therapies for COPD are based on anti-inflammatory drugs and bronchodilators which only help to minimize the airflow limitation and prevent acute exacerbations, oxygen administration, and lung transplantation in advanced disease stages. Currently there are no disease modifying treatments that prevent or correct the progressive tissue destruction in lung disease, and thus novel regenerative medicine approaches are needed.

RATIONALE AND EXPERIMENTAL EVIDENCE FOR CELL-BASED THERAPIES FOR COPD

Cell-based therapies are a novel and promising therapeutic approach that has been extensively studied for a diverse group of diseases. In this context mesenchymal stromal cells (MSCs) have been widely investigated in chronic and acute respiratory diseases. MSCs are non-epithelial, non-hematopoietic progenitors that under specific conditions can be derived from bone marrow and potentially other tissues although the equivalence of MSCS from different tissues is of intense scientific debate. Epithelial cells are a more likely beneficial form of cell-based therapy, yet studies with epithelial cell delivery have not been performed in clinical trials nor in sufficient pre-clinical studies.

There is some preclinical evidence supporting the therapeutic capacity of MSCs which has shown changes in the expression profiles of genes responsible for immune responses with decreased inflammation and improvement of pulmonary function (Reviewed in Antunes et al., 2017; Weiss, 2018). However, the mechanisms through which MSCs mediate these responses are not fully understood. The initial hypothesis that the systemic or intratracheally administered MSCs were engrafting in the lung is unlikely; evidence suggests that MSCs work by a paracrine mechanism of immunomodulation. Regardless of the potential mechanism, a beneficial effect of MSCs in patients with lung disease remains unproven. Concerns include differences in methods to derive and deliver MSCs as well as contradicting results obtained by different groups. (Reviewed in Antunes et al. 2017; Weiss, 2018; Ikonomou et al., 2019). The development of strategies to expand and deliver epithelial cells for therapy remains at the basic research stage.

WHAT IS THE CLINICAL STATUS OF CELL-BASED THERAPIES FOR COPD?

Results of preclinical studies with MSCs increased the interest of many research groups to start clinical research on systemic MSC administration for the treatment of different lung diseases. Initial trials of systemic administration of MSCs in patients focused on safety. In 2013, Weiss et al. published results from a randomized double-blinded phase I study of allogenic MSCs in COPD, showing that intravenous treatment with non-human leukocyte antigen-matched allogenic MSCs was safe in COPD patients but

did not show improvement of lung function, lung inflammatory markers, exercise capacity or quality of life. Interestingly this study documented a significant reduction in circulating C reactive protein (CRP) levels, suggesting that MSCs could decrease systemic inflammation. Similar effects on inflammation were observed in a more recent phase I study in which 10 patients with advanced emphysema were treated with allogenic MSCs delivered intratracheally (de Oliveira et al. 2017); results from this study also showed improvement in body mass index, airway obstruction, exercise capacity and quality of life. These and other clinical trials that have tested MSC treatment have different criteria for the stage of the disease and characteristics of the population to be included. At present, there is no established scientific consensus for the source (different studies have used bone marrow, adipose, or placenta-derived MSCs), dose or method of delivery of MSCs (some studies use intratracheal cell delivery while some use intravenous administration). These differences could explain the variability in the reported outcomes and at the same time make the analysis and comparison of all results challenging (Ikonomou, 2019). Further studies are needed with standardized criteria and methods that can help move the field of cell therapy for lung disease forward.

Patients need to understand that additional concerns regarding MSC-based therapy for lung disease include the lack of proper regulation of current studies. Listing of clinical studies on clinicaltrials.gov does not mean there has been proper regulatory oversight. It is also important to note that there are no MSC-based therapies of any kind approved in the US. A recent statement by the American Thoracic Society is an excellent resource for the current state of cell therapy for lung disease.

WHAT DOES THE NEAR FUTURE HOLD?

While cell-based therapy could become a viable treatment option for clinical application for lung disease in the future, there is no definitive evidence that these cells have a therapeutic benefit. Furthermore, there are still many significant factors to be considered in any future trials such as the best source of MSCs; the route of administration and the most effective dose to trial before MSC administration is considered a safe and effective treatment option. More basic research is needed to further develop the possible use of epithelial cells as a cell-based therapy for lung disease, even before clinical trials can be done.

At present there are no licensed cell-based therapies for lung diseases in the U.S or globally (Ikonomou et al 2019; Sipp et al. 2017). It is critical that patients are well informed regarding the current lack of efficacious cell-based therapeutic options. Patients considering such treatments need to understand that current cell-based therapies for lung disease are unproven, experimental, and are not under appropriate regulatory oversight.

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RECOMMENDED READINGS AND LINKS

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