

Update and Arizona Thoracic Society Position Statement on Stem Cell Therapy for Lung Disease

Summary

Infusions of stem cells are increasingly being offered for a variety of diseases, including chronic lung diseases such as chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF) and cystic fibrosis. However, the potential for harm, the lack of any proven benefit, and the high fees that many of these programs charge make recommending stem cell therapy untenable. At the time of this writing (April 2019) it appears that stem cell therapy can be safely performed, although the long-term side effects remain unknown. However, the little data available show no benefit in meaningful outcomes, such as mortality, morbidity or patient well-being, for stem cell treatment of chronic lung disorders. Patients with severe, incurable diseases may be motivated to seek innovative therapies. We encourage such patients to contact their primary care physician or pulmonologist. Clinical trials in the United States and Canada investigating stem cell therapy for lung diseases can be found on the website of the National Institutes of Health at Clinicaltrials.gov. The Arizona Thoracic Society encourages regulatory agencies to protect the public health and take appropriate action against non-investigational, for-profit stem cell clinics when appropriate.

Introduction

A central component of the mission of medical societies is to translate new scientific information into patient education. There appears to be increasing direct-to-consumer advertising of untested, unapproved, and potentially ineffective “stem-cell” treatments for a variety of diseases, including lung disorders (1). One may come across information regarding stem cell therapy for chronic obstructive pulmonary disorders and fibrotic lung disease, in the United States and worldwide, on the internet, patient support groups, or other sources. Recently, a direct mailing to the home of one of the members of the Arizona Thoracic Society was received (Figure 1).



Figure 1. Direct mailing for stem cell therapy for several diseases including COPD received by one of the members of the Arizona Thoracic Society.

- These programs are often characterized by:
- Exorbitant fees
- Misrepresentation of risks and benefits
- Overreliance on, and advertisement of, patient testimony
- Poor patient follow-up
- Absence of regulatory oversight and objective clinical evidence for claimed benefits

Therefore, they differ substantially from therapies approved by legitimate regulatory agencies, from well-designed, controlled, and appropriately regulated clinical trials, and from regulated compassionate use of innovative cell therapies.

Chronic Obstructive Pulmonary Disease (COPD)

Stem cells can differentiate into several different lung cell types, including the alveolar epithelial cells. Since COPD is a disease associated with destruction of alveoli induced by cigarette smoke, the concept of rebuilding the alveoli through stem cell therapy is attractive. Pre-clinical trials in animal models have suggested regeneration of alveolar-like structures, repair of emphysematous lungs, and reduction of inflammatory responses, with the greatest success being in acute lung injury models.

Currently, regenerative therapies are divided into extrinsic therapeutic strategies and intrinsic cell therapy methods. Extrinsic cell therapy refers to the vascular infusion of (or endotracheal installation) of stem cells, including embryonic stem cells (ESCs), induced pluripotent stem cells (iPSs), mesenchymal stem cells (MSCs), and human lung stem cells (hLSCs). Intrinsic therapy refers to the delivery of small molecules (retinoid compounds have been the most studied) that can stimulate the endogenous lung stem/progenitor cells to regenerate and replace damaged structures.

A number of recent review articles have summarized the current state of research in the use of stem cells in COPD (2-4). These review articles all contain summaries of trials conducted to date using both extrinsic and intrinsic therapies. There have been several phase I clinical trials, primarily assessing safety, and a handful of small phase II clinical trials that have been negative for meaningful clinical outcomes. Sun *et al.* (3) point out that the available trials have all been conducted on patients with advanced COPD. The authors suggest that further research is required on how to enhance the engraftment of exogenous mesenchymal stem cells in damaged lungs. Further, considering the anti-inflammatory and immunomodulatory effects of exogenous mesenchymal stem cells, they may be most effective potentially in treating acute lung disease, as opposed to chronic progressive disease with severe structural damage.

Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is a progressive debilitating lung disease of unknown etiology characterized by a combination of histological changes, including extracellular matrix (ECM) deposition, phenotypic changes of fibroblasts, and alveolar epithelial cells, the formation of fibroblastic foci, and scattered areas of aberrant wound healing interspersed with normal lung parenchyma (5).

There are two approved compounds for the treatment of IPF: pirfenidone and nintedanib. Pirfenidone is an antifibrotic compound with an unclear mechanism of action, targeting several molecules, including transforming growth factor- β (TGF- β), tumor necrosis factor- α (TNF- α), and interleukin 6 (6). Nintedanib is a tyrosine-kinase inhibitor, targeting vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR), and platelet derived growth factor receptor (PDGFR) (7). While the use of pirfenidone and nintedanib has been shown to slow the progression of IPF, neither is curative and morbidity and mortality from IPF remains high (8,9).

Because of the inadequacy of therapy in IPF, the use of mesenchymal stem cells (MSCs) has attracted interest as a potential option. Early clinical studies have shown that the MSCs can be safely administered (5,10-12). A phase Ib study of endobronchially administered autologous adipose-derived MSCs showed not only acceptable safety outcomes, but also improvements in quality of life parameters (12). However, there were no significant differences in any of the studied functional parameters (FVC, FVC%pred. and DLCO% pred.) at baseline and 6 and 12 months following 3 endobronchial infusions of MSCs.

Cystic Fibrosis

Cystic fibrosis (CF) is a genetic syndrome usually resulting in a high mortality rate due to progressive lung disease. Several drugs targeting specific mutated cystic fibrosis transmembrane regulator (CFTR) proteins are already in clinical trials. However, new therapies, based on stem cells, are also emerging. Interest has focused on induced pluripotent stem (iPS) cells. It is possible to make iPS cells using cells from people with CF, and then use gene editing to correct CFTR mutations in those cells (13). This suggests the possibility of re-implanting the corrected iPS cells into the lungs of people with CF to generate healthy lung cells. Currently, three trials examining the safety of stem cells in cystic fibrosis are ongoing according to Clinicaltrials.gov.

Adult Respiratory Distress Syndrome (ARDS)

Four clinical trials are listed on Clinicaltrials.gov for ARDS and stem cells; one, which involved 3 patients, has been completed (14). No outcome information is available.

Other Lung Diseases

We are unaware of any human trials at this time with outcomes in other lung diseases.

Regulatory and Legal Actions

The Food and Drug Administration (FDA) and the Attorney General of New York have both expressed concern over stem cell therapy. The concerns follow reports of three patients becoming blind after receiving injections of stem cells into the eye and twelve patients who became seriously ill after receiving injections that purportedly contained stem cells from umbilical cord blood (15,16). The FDA has issued warning letters to stem cell clinics, including one letter claiming violation of Federal law, and another 20 warnings to clinics of that their claims and actions were subject to FDA approval. The NY Attorney has filed a lawsuit against a for-profit stem cell clinic, Park Avenue Stem Cell, claiming it performed unproven procedures on patients with a wide range of medical conditions, from erectile dysfunction to heart disease (17).

The Arizona Thoracic Society encourages further investigation into stem cell transplantation in lung disease. However, we do not at this time encourage non-investigational use of stem cells since the therapy has not been shown to have meaningful patient benefits. We also encourage state and local regulatory agencies in the Southwest to protect the public health and take appropriate action against non-investigational, for-profit stem cell clinics when appropriate.

References

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