3-7-2023

Moving Senolytics Closer to the Clinic in IPF

Daniel Kramer
Thomas Jefferson University

Gautam George
Thomas Jefferson University

Ross Summer
Thomas Jefferson University

Moving senolytics closer to the clinic in IPF

Daniel Kramer,[a,b] Gautam George,[a,b] and Ross Summer[a,b,*]

[a]Sidney Kimmel Medical College at Thomas Jefferson University, USA
[b]The Jane and Leonard Korman Respiratory Institute at Thomas Jefferson University, USA

eBioMedicine
2023;90: 104513
Published Online xxx
https://doi.org/10.1016/j.ebiom.2023.104513

Idiopathic Pulmonary Fibrosis (IPF) is a life-threatening respiratory condition with few effective treatments and occurs almost exclusively in older individuals. The median age of onset is approximately 60 years of age and its incidence and prevalence increases dramatically after the sixth decade of life.[1] Consistent with this, and similar to other conditions that primarily affect older individuals, such as cardiovascular disease, diabetes and Alzheimer's disease,[1] IPF is now considered an age-related disorder of the lung. Along these lines, epithelial cells, fibroblasts and macrophages from the IPF lung exhibit major "hallmarks" of pathologically aging tissues, such as altered intracellular communication, genomic instability, telomere attrition, progenitor cell exhaustion, loss of proteostasis, altered nutrient sensing, mitochondrial dysfunction and cellular senescence.[2,3]

As aging plays a role in IPF, researchers have begun exploring strategies to slow, arrest or even reverse the aging process. One such approach is to eliminate senescent cells using senolytic therapies.[4,5] Senescent cells are cells that have undergone stress-induced cell cycle arrest. These cells are known to accumulate in IPF and contribute to the initiation and progression of pulmonary fibrosis in experimental models. Since senescent cells do not divide or respond to mitogenic stimuli their presence is thought to contribute to disease, in part, by limiting epithelial repair.[3] Moreover, senescent cells secrete various cytokines, chemokines and growth factors that can promote inflammation and drive the production of extracellular matrix molecules, factors important for the formation of IPF fibrotic scars.

The concept of targeting senescent cells in IPF has arisen from research in other age-related diseases. Indeed, senolytic therapies have been shown to alleviate senescence/age-related disorders in models of atherosclerosis, osteoporosis, hepatic steatosis and Alzheimer's disease. In recent studies the combination of Dasatinib (D) and Quercetin (Q) has shown promising results as a senolytic therapy in animal models. These drugs act by inhibiting tyrosine kinases, which are enzymes that happen to also be targeted by the existing FDA-approved IPF therapy nintedanib. DQ therapy has been shown to be highly effective in eliminating senescent cells, including in models of pulmonary fibrosis.[6] DQ treatment has also been found to significantly improve lung function and physical health in a mouse model of pulmonary fibrosis,[6] providing support for testing its therapeutic potential in human fibrotic lung diseases.

In the recent issue of *eBioMedicine*, Nambiar and Kellogg and colleagues bring DQ therapy closer to the clinic by reporting the results of a small, phase I trial of DQ in IPF patients.[7] This study is the first randomized, placebo-controlled trial of DQ in IPF and provides evidence for the feasibility of larger clinical trials in this disease. Although the trial has important limitations, such as a small sample size (12 IPF patients) and a short duration of observation (13 weeks), results suggest that DQ is safe and does not lead to an increase of severe adverse events (AE). However, authors did report on an increase in non-serious AEs, including feeling unwell, cough, nausea, fatigue, weakness, and headache. While these side effects do not pose life-threatening consequences, we worry that these complaints could ultimately limit compliance with DQ therapy. For instance, cough is already a problem for many IPF patients and gastrointestinal side effects remain a major factor limiting the tolerability of existing IPF anti-fibrotic treatments.

In conclusion, this phase I trial provides additional support for the investigation of senolytics in the treatment of IPF. While this trial is too small to draw conclusions about long term safety or efficacy or to determine the impact of DQ on the burden of senescent cells in the IPF lung, larger studies may help add this novel approach to the limited arsenal of treatments for IPF patients.

Contributors
Drs Kramer, George and Summer contributed equally to the writing of this commentary. All the authors read and approved the manuscript.

Declaration of interests
None.

Acknowledgements
Funding: None.

DOI of original article: https://doi.org/10.1016/j.ebiom.2023.104481
*Corresponding author. Department of Medicine, Division of Pulmonary, Allergy and Critical Care and the Center for Translational Medicine; the Jane & Leonard Korman Respiratory Institute, Philadelphia, PA, USA.
E-mail address: Ross.Summer@Jefferson.edu (R. Summer).

References

1 Lederer DJ, Martinez FJ. Idiopathic pulmonary fibrosis. *N Engl J Med*. 2018;378:1811–1823.
2 Gulati S, Thannickal VJ. The aging lung and idiopathic pulmonary fibrosis. *Am J Med Sci*. 2019;357:384–389.
3 López-Otín C, Blasco MA, Partridge L, et al. The hallmarks of aging. *Cell*. 2013;6:1194–1217.
4 Justice JN, Nambiar AM, Tchkonia T, et al. Senolytics in idiopathic pulmonary fibrosis: results from a first-in-human, open-label, pilot study. *eBioMedicine*. 2019;40:554–563.
5 Chaib S, Tchkonia T, Kirkland JL. Cellular senescence and senolytics: the path to the clinic. *Nat Med*. 2022;28:1556–1568.
6 Schafer MJ, White TA, Iijima K, et al. Cellular senescence mediates fibrotic pulmonary disease. *Nat Commun*. 2017;23:14532.
7 Nambiar A, Kellogg D, Justice J, et al. Senolytics dasatinib and quercetin in idiopathic pulmonary fibrosis: results of a phase I, single-blind, single-center, randomized, placebo-controlled pilot trial on feasibility and tolerability. *eBioMedicine*. 2023. https://doi.org/10.1016/j.ebiom.2023.104481.