although the influence of side effects should also be taken into consideration because it could lead to hospitalizations related to deconditioning. However, the use of antifibrotics in patients with non-IPF ILD is an indicator of progressive behavior and might therefore be associated with higher rates of hospitalization. Notably, the concept of progressive pulmonary fibrosis has been discussed and defined during the observation time of the study (5–7). Consequently, the authors probably had no possibility to discriminate between patients with non-IPF progressive and nonprogressive pulmonary fibrosis according to the recent guidelines (7), which is crucial for the indication to start an antifibrotic treatment in progressive pulmonary fibrosis. Thus, even if relevant, the effect of antifibrotic treatment on hospitalizations remains to be fully clarified and may deserve a more accurate definition of respiratory-related events, needing to be more focused on acute exacerbation. The feasibility and practicality of using hospitalizations as a primary endpoint in ILD clinical trials also raise logistical concerns, because larger sample sizes and prolonged study periods could be required to accumulate enough events and provide sufficient statistical power (8). This temporal challenge may conflict with the urgency to bring novel therapies to market, demanding a delicate balance between scientific rigor and timely clinical translation.

In conclusion, the study by King and colleagues significantly expands the current knowledge on hospitalization rates and outcomes in patients with ILD. However, the true impact of hospitalizations in distinct ILD populations, as well as the precipitating causes of these events, should be further clarified. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Giacomo Sgalla, M.D., Ph.D.
Universita` Cattolica del Sacro Cuore
Rome, Italy
and
Dipartimento di Neuroscienze, Organi di Senso e Torace
Fondazione Policlinico Universitario A. Gemelli Istituto Di Ricovero e Cura a Carattere Scientifico
Rome, Italy

Elena Bargagli, M.D., Ph.D.
Dipartimento di Scienze Mediche, Chirurgiche e Neuroscienze
Università di Siena
Siena, Italy

ORCID ID: 0000-0003-3130-9388 (G.S.).

References

1. Kim HJ, Snyder LD, Adegunsoye A, Neely ML, Bender S, White ES, *et al.*; IPF-PRO Registry Investigators. Hospitalizations in patients with idiopathic pulmonary fibrosis. *Respir Res* 2021;22:257.
2. Wälscher J, Witt S, Schwarzkopf L, Kreuter M. Hospitalisation patterns of patients with interstitial lung disease in the light of comorbidities and medical treatment - a German claims data analysis. *Respir Res* 2020; 21:73.
3. Brown AW, Fischer CP, Shlobin OA, Buhr RG, Ahmad S, Weir NA, *et al.* Outcomes after hospitalization in idiopathic pulmonary fibrosis: a cohort study. *Chest* 2015;147:173–179.
4. King CS, Ignacio RVMS, Khangoora V, Nyquist A, Singhal A, Thomas C, *et al.* Hospitalization rates in interstitial lung disease: an analysis of the Pulmonary Fibrosis Foundation Registry. *Am J Respir Crit Care Med* 2024;210:801–813.
5. Cottin V, Hirani NA, Hotchkin DL, Nambiar AM, Ogura T, Otaola M, *et al.* Presentation, diagnosis and clinical course of the spectrum of progressive-fibrosing interstitial lung diseases. *Eur Respir Rev* 2018;27: 180076.
6. George PM, Spagnolo P, Kreuter M, Altinisik G, Bonifazi M, Martinez FJ, *et al.*; Erice ILD working group. Progressive fibrosing interstitial lung disease: clinical uncertainties, consensus recommendations, and research priorities. *Lancet Respir Med* 2020;8:925–934.
7. Raghu G, Remy-Jardin M, Richeldi L, Thomson CC, Inoue Y, Johkoh T, *et al.* Idiopathic pulmonary fibrosis (an update) and progressive pulmonary fibrosis in adults: an official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2022;205: e18–e47.
8. King TE Jr, Albera C, Bradford WZ, Costabel U, du Bois RM, Leff JA, *et al.* All-cause mortality rate in patients with idiopathic pulmonary fibrosis. Implications for the design and execution of clinical trials. *Am J Respir Crit Care Med* 2014;189:825–831.

Unraveling the Complexities of Mesenchymal Stromal Cell-based Therapies: One Size Doesn't Fit All

Cell-based therapy utilizing mesenchymal stromal cells (MSCs) is an exciting and promising potential approach for lung diseases and critical illnesses. The rationale is based on a robust platform in which MSCs isolated from bone marrow, adipose, placental, and other tissues can, after either systemic or direct airway administration, ameliorate inflammation and injury in a wide range of preclinical disease models in both small and large animals (1, 2). Mechanistically, the MSCs are believed to exert protective and reparative effects through release of a range of paracrine mediators, including, but not limited to, antiinflammatory cytokines, growth factors, and extracellular vesicles (3). Other actions—for example, mitochondrial transfer—may also play a role (4).

This platform has led to a growing number of clinical investigations in a range of lung diseases and critical illnesses including both non–coronavirus disease (non–COVID-19) and

Originally Published in Press as DOI: 10.1164/rccm.202405-0961ED on June 6, 2024

COVID-19–associated acute respiratory distress syndrome and bronchopulmonary dysplasia (BPD) (5, 6). Although some trials have demonstrated benefit, not all have done so, and the ongoing challenge is to better devise optimal strategies for MSC use that incorporate a better mechanistic understanding of MSC actions in different diseases. Unresolved issues include source and optimal approaches for *ex vivo* expansion of the MSCs, dose, and dosing regimen. Of increasingly recognized importance, the patient inflammatory phenotype within any given disease entity also significantly affects MSC actions and, thus, potential therapeutic effects (7). The latter reflects the growing appreciation that the MSCs—by virtue of expressing cell surface damage and pathogen-associated molecular pattern receptors, such as the Toll-like receptors—respond to different inflammatory environments by altering their paracrine profile (8). The inflammatory environment also influences MSC clearance. Systemically administered MSCs lodge in the pulmonary capillary bed, where they are cleared over approximately 1–2 days through efferocytosis, apoptosis, and other host immune mechanisms (8). While lodged, they do not engraft but rather respond to the local inflammatory environment, with the resulting release of different profiles of paracrine mediators (9, 10). Some data also suggest that it is the host response to the MSCs that drives the observed beneficial effects rather than direct effects of the MSCs themselves (11, 12).

Another confounding factor is that MSCs isolated from any given tissue source themselves constitute a heterogenous population of cells with different attributes and potential therapeutic implications. This has confounded efforts to date to determine benchmarks for MSC "potency" for any given application. To this end, in this issue of the *Journal*, the study by Cyr-Depauw and colleagues (pp. 814–827) conducted at the Ottawa Hospital Research Institute provides important new information that helps to discriminate different populations utilizing as their model MSCs derived from umbilical cord blood samples from 5 healthy term donors (13). This is a leading group investigating potential MSC therapeutic approaches for BPD and other diseases. The underlying rationale was that single-cell transcriptomic profiling would identify different MSC populations with different protective and reparative effects. The investigators accordingly present robust data that discriminate the MSCs into two populations, one of which exhibited progenitor characteristics, enriched in genes with functions related to cell division, cell cycle, cell proliferation, DNA transcription, and chromatin organization. The other identified population was comprised of MSCs with fibroblast-like characteristics marked by high expression of genes related to extracellular matrix organization and collagen metabolism. It is interesting that four of the five donor samples exhibited the progenitor transcriptome, whereas the fifth was more fibroblastic. These observations correlate with some previously published data from other groups (14); however, the important step taken here was to then interrogate the different MSC populations in a preclinical rat model of BPD utilizing hyperoxia exposure. The investigators found that the MSCs with progenitor attributes were more protective than those with fibroblastic characteristics and further identified the differential expression of HLA-ABC between these groups as a discriminant that affected both MSC retention in the lung and protective effects. Differential expression of HLA gene expression and cell surface markers has also been observed in other studies in which human bone marrow–derived MSCs were exposed to clinical BAL samples from patients with acute respiratory distress syndrome versus lavage samples from healthy volunteers (15).

All told, the present study by Cyr-Depauw and colleagues provides further evidence that more mechanistic information is required for best clinical implementation of MSC-based cell therapies. In parallel, better understanding of cell therapy manufacturing to regulate production of MSCs with differing abilities is an area of active investigation. There are some limitations to the study, including that MSCs with progenitor attributes from only one of the four donors was assessed in the BPD model. These observations will need to be expanded in more wide-ranging studies. Nonetheless, the present data are an important advance in bringing MSC-based cell therapies to successful clinical use. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Daniel J. Weiss, M.D., Ph.D.
Department of Medicine
and
Department of Bioengineering
University of Vermont
Burlington, Vermont

References

1. Ting AE, Baker EK, Champagne J, Desai TJ, dos Santos CC, Heijink IH, *et al.* Proceedings of the ISCT scientific signature series symposium, "Advances in cell and gene therapies for lung diseases and critical illnesses." *Cytotherapy* 2022;24:774–788.
2. Curley GF, O'Kane CM, McAuley DF, Matthay MA, Laffey JG. Cell-based therapies for acute respiratory distress syndrome: where are we now? *Am J Respir Crit Care Med* 2024;209:789–797.
3. Galipeau J, Sensébé L. Mesenchymal stromal cells: clinical challenges and therapeutic opportunities. *Cell Stem Cell* 2018;22:824–833.
4. Islam MN, Das SR, Emin MT, Wei M, Sun L, Westphalen K, *et al.* Mitochondrial transfer from bone-marrow-derived stromal cells to pulmonary alveoli protects against acute lung injury. *Nat Med* 2012;18: 759–765.
5. Kirkham AM, Monaghan M, Bailey AJM, Shorr R, Lalu MM, Fergusson DA, *et al.* Mesenchymal stem/stromal cell-based therapies for COVID-19: first iteration of a living systematic review and meta-analysis: MSCs and COVID-19. *Cytotherapy* 2022;24:639–649.
6. Thébaud B. Stem cell therapies for neonatal lung diseases: are we there yet? *Semin Perinatol* 2023;47:151724.
7. Martin TR, Zemans RL, Ware LB, Schmidt EP, Riches DWH, Bastarache L, *et al.* New insights into clinical and mechanistic heterogeneity of the acute respiratory distress syndrome: summary of the Aspen Lung Conference 2021. *Am J Respir Cell Mol Biol* 2022;67:284–308.
8. Waterman RS, Tomchuck SL, Henkle SL, Betancourt AM. A new mesenchymal stem cell (MSC) paradigm: polarization into a pro-inflammatory MSC1 or an immunosuppressive MSC2 phenotype. *PLoS One* 2010;5:e10088.
9. Kusuma GD, Carthew J, Lim R, Frith JE. Effect of the microenvironment on mesenchymal stem cell paracrine signaling: opportunities to engineer the therapeutic effect. *Stem Cells Dev* 2017;26:617–631.
10. Abreu SC, Rolandsson Enes S, Dearborn J, Goodwin M, Coffey A, Borg ZD, *et al.* Lung inflammatory environments differentially alter mesenchymal stromal cell behavior. *Am J Physiol Lung Cell Mol Physiol* 2019;317:L823–L831.
11. Weiss DJ, English K, Krasnodembskaya A, Isaza-Correa JM, Hawthorne IJ, Mahon BP. The necrobiology of mesenchymal stromal cells affects therapeutic efficacy. *Front Immunol* 2019;10:1228.

12. de Witte SFH, Luk F, Sierra Parraga JM, Gargesha M, Merino A, Korevaar SS, *et al.* Immunomodulation by therapeutic mesenchymal stromal cells (MSC) is triggered through phagocytosis of MSC by monocytic cells. *Stem Cells* 2018;36: 602–615.
13. Cyr-Depauw C, Cook DP, Mižik I, Lesage F, Vadivel A, Renesme L, *et al.* Single-cell RNA sequencing reveals repair features of human umbilical cord mesenchymal stromal cells. *Am J Respir Crit Care Med* 2024;210:814–827.
14. Wang Q, Li J, Wang S, Deng Q, Wang K, Dai X, *et al.* Single-cell transcriptome profiling reveals molecular heterogeneity in human umbilical cord tissue and culture-expanded mesenchymal stem cells. *FEBS J* 2021;288:5311–5330.
15. Enes SR, Hampton TH, Barua J, McKenna DH, dos Santos CC, Amiel E, *et al.* Healthy *versus* inflamed lung environments differentially affect MSCs. *Eur Respir J* 2021;58:2004149.