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Idiopathic Pulmonary Fibrosis: A Degenerative Disease Requiring a Regenerative Approach Reply

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and traditional pharmacologics with progenitor cell activity, informed by our basic science colleagues—will transform treatment options for patients with IPF in decades to come.

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Reply

From the Authors:

We thank Drs. Tzouvelekis, Bouros, Chambers, and Hopkins for their interest in our article (1). We agree that a number of challenges must be addressed to design a safe and potentially effective trial of mesenchymal stem cells (MSCs) for the treatment of idiopathic pulmonary fibrosis (IPF).

In their letter, Drs. Tzouvelekis and Bouros highlight six of these challenges. We will discuss these important concerns.

1. The disease biology of IPF is complex and poorly understood. Multiple drug regimens have been tested and none found to favorably alter clinical outcomes. In fact, a recent trial showed an increase in IPF mortality with immunosuppressive therapy (2). Accordingly, we continue to have no treatments approved by the U.S. Food and Drug Administration for IPF and, therefore, have nothing to offer patients facing an inexorable decline in lung function. Because several preclinical studies (primarily utilizing the murine bleomycin model) suggest that MSCs might be efficacious in the treatment of IPF (Table 1 of our article) and because their safety profile in humans has been favorable (Table 2 of our article), we suggest that it is time to move ahead with phase I trials of MSCs for IPF. While we agree that adverse effects are possible, it is for exactly that reason we propose to begin with a trial of safety rather than efficacy.
2. As with all studies of IPF, clinical trial participant recruitment and selection will be a challenge given the clinical heterogeneity of the disease and because most patients present with advanced disease. With regard to cell therapy, preclinical studies suggest that MSCs may be most efficacious during the "early inflammatory" stage of IPF and less so in the setting of established fibrosis (3). While this may also be true in humans, it is important to remember that unlike the murine bleomycin model, IPF is characterized by areas of ongoing lung and epithelial injury with adjacent established areas of fibrosis. In addition, data from cardiac studies suggest the potential for MSCs to reverse remodeling and to decrease the size of ischemia-induced scar tissue, supporting the possibility that MSCs can exert antifibrotic effects when fibrosis is established (4, 5).
3. The selection of appropriate endpoints for phase II and III trials of MSCs in IPF will be critical. Given the advanced stage at which most patients present, we agree that significant improvements in lung function may be difficult to demonstrate. However, using appropriately chosen measures of lung function, it may be possible to demonstrate an effect on disease progression, quality of life, and perhaps even survival. Certainly the concomitant study of biomarkers will be vital to understanding the role of cell therapy in modulating disease progression (6).
4. A phase I trial evaluating the safety of MSCs in IPF should begin with a single infusion. Once safety has been established, the question of single versus repeated infusions will need to be addressed. While cardiac studies have demonstrated an effect with single infusions (7), it is unclear if this will also be the case in the lungs and therefore further study will be needed.
5. The most optimal route of administration of MSCs for IPF is also unknown. Cell tracking studies demonstrate that intravenously administered cells localize primarily to the lung (8), suggesting that this first pass phenomenon by which cells become trapped in small capillaries may make intravenous administration ideal for lung disease. That said, other routes of administration, such as endobronchial, may have merit and testing of this hypothesis is warranted (9).
6. The most optimal source of MSCs (autologous versus allogeneic, bone marrow derived versus adipose, placental, or other) will also require further study. Safety profiles, efficacy, and ease of acquisition will all be important determinants of the most ideal source of cells, and we certainly favor continued investigation (10).

We also appreciate the input of Drs. Chambers and Hopkins and could not agree more on the importance of separating "safety from efficacy and hype from hope." IPF is a devastating disease for patients and families alike—one with no treatment options. While the ultimate goal of cell-based therapies is disease modification, early trials should, and must, focus on safety. To that end, we eagerly anticipate the results of their phase I trial of placenta derived MSCs for the treatment of IPF. We also agree that continued collaboration between basic scientists and clinicians will be needed to better understand the pathogenesis of IPF and how this informs our design of novel therapeutic interventions.

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Assessment of Endobronchial Ultrasound-guided Transbronchial Needle Aspiration Performance

To the Editor:

As researchers in assessment of clinical procedures and pulmonary endosonography, we have read the article by Dr. Davoudi and colleagues (1) with great interest, as objective measurement of novel technical skills is important. We argue that three issues deserve specific attention.

The reported reliability of 0.9991 is extremely high, and several factors should be considered when interpreting this finding. The theoretical part of the assessment tool should be omitted from the reliability calculations as the correct answers are predefined, which always results in 100% interrater agreement, which will increase the agreement of the whole test. Additionally, these items can only be tested once, and therefore the instrument cannot be used in this form to test multiple procedures. Furthermore, the performance test was administered to a very heterogeneous group of subjects, which always improves reliability (2), and was scored by two colleagues who have worked closely together for many years and had intimate knowledge of the assessment tool. Before generalizing these results, we recommend testing the tool on a group of trainees using different raters and analyzing the results using generalizability theory.

Second, each participant was only tested once, which made it impossible to explore the variance in individual performance. From motor skills learning theory, it is well known that the performances of trainees are highly variable, especially in the first, *cognitive*, stage (3). In a recent study of endoscopic ultrasonography competence in pulmonary patients, we found that assessment of at least four procedures was necessary to provide reliable results (4). It would be unwise to base important decisions on the administration of a single test.

Finally, it is a limitation that the assessment tool can only be used under direct observation. Observational assessment is subject to all of the potential pitfalls of human relations: subjectivity, false impressions, the three "isms" (ageism, racism, and sexism), rumor, grudge, and misinterpretation (5). A review of 104 studies of objective assessment of technical surgical skills used the Oxford Centre for Evidence-based Medicine levels of evidence where high levels of evidence required blinded reference standards (6). For high-stakes assessment (certification and recertification) and research in medical education (e.g., comparisons between traditional and simulation-based education), we recommend an assessment tool that can be used in a blinded fashion, that is, using video recordings of the procedures.

The above-mentioned issues aside, we acknowledge the important work of this study, which is another step forward in implementing endosonography in pulmonary medicine.

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