Hospitalizations as Clinical Trials Endpoint in Interstitial Lung Disease

Are We There Yet?

Despite the progress made in understanding the pathogenesis of idiopathic pulmonary fibrosis (IPF) and other forms of interstitial lung disease (ILD), predicting the clinical course of these patients remains challenging. The trajectory of patients with ILD is punctuated by hospitalizations, which are recognized as clinically impactful events for being associated with significant morbidity and mortality. Nevertheless, diverse hospitalization rates of IPF have been reported in the literature, and scarce evidence exists regarding the hospitalization rates of other forms of ILD. Moreover, most studies relied on retrospective databases and registries, which are intrinsically limited by poor reliability with regard to the definition of the causes of hospitalization (1–3). As such, the interpretation of the true prognostic significance of hospitalization has remained pretty much elusive so far.

In this issue of the *Journal*, King and colleagues (pp. 801–813) describe the findings of a comprehensive analysis of hospitalizations among various ILDs, leveraging the opportunity presented by the Pulmonary Fibrosis Foundation (PFF) Patient Registry, which encompasses a large, diverse cohort of participants with ILD from PFF care centers across the United States (4). The study analyzed data collected from 2016 to 2021 from almost 2,000 patients stratified into distinct ILD subtypes, including IPF, non-IPF idiopathic interstitial pneumonia (IIP), connective tissue disease–related ILD (CTD-ILD), chronic hypersensitivity pneumonitis (CHP), and other ILDs, with the aim of expanding the current knowledge of hospitalization rates and outcomes across the ILD spectrum. However, no data were available concerning the radiological and/or histopathological patterns of disease.

The key findings underscore the high prevalence of hospitalizations in participants with ILD: more than one-third of the patients (35%) experienced hospitalization events, most (60%) of which were for respiratory-related causes. Interestingly, comparable hospitalization rates were found across different ILDs, challenging the assumption that IPF may be characterized by distinct hospitalization patterns because of worse prognosis. Delving into the factors associated with higher risk of hospitalizations, the need for supplemental oxygen, treatment with immunosuppression, congestive heart failure, and percent predicted D_{LCO} were identified as significant predictors of all-cause and respiratory-related hospitalization events. In the subgroup of patients with IPF, the use of antifibrotics at enrollment was most common in patients experiencing respiratory-related hospitalizations, although the lack of data on therapeutic management at follow-up (such as commencement of new therapies or treatment discontinuation) make it impossible to draw conclusions on such a relationship. With regard to the clinical implications of hospitalizations, respiratory-related hospitalizations stood out as robust indicators of poor outcomes, being independently associated with reduced transplant-free survival. Importantly, hospitalization duration exceeding 5 days was found to be associated with a twofold increase in the risk of death or transplant, suggesting that longer hospital stay may represent a surrogate for causes that are less prone to being reversible, such as ILD progression or acute exacerbation. At the comparative analysis of outcomes after hospitalization among different ILD subtypes, CTD-ILD, CHP, and non-IPF IIP exhibited superior transplant-free survival compared with IPF, possibly reflecting the better response to treatment of precipitating causes of hospitalization and the slower progression of the underlying fibrotic disease.

Indeed, King and colleagues should be congratulated for their effort to provide further insight into the complex clinical scenario of hospitalizations in ILD. The main strength of this study lies in the use of the PFF Patient Registry, which allowed the authors to capture real-world data from a broad, well-characterized ILD population. Unlike previous studies predominantly focused on IPF, King and colleagues offered a more comprehensive snapshot of hospitalization patterns in ILD. In light of the study's findings, the authors place emphasis on respiratory-related hospitalizations as a meaningful surrogate outcome for mortality, suggesting that incorporating respiratory-related hospitalizations as an endpoint could enhance the effectiveness of clinical trials in ILD, especially if coupled with factors associated with higher risk for hospitalization, including longer hospital stay.

Nevertheless, the study by King and colleagues is also characterized by inherent limitations because of its retrospective design, and it fails in disentangling the specific causes leading to hospitalization. A more accurate stratification of hospitalizations would be pivotal to validate their role as a clinical trial endpoint, because not all respiratory-related hospitalizations carry the same weight in terms of clinical significance, treatment responses, and prognosis. Moreover, the use of hospitalizations as an endpoint might not be the right fit for all ILD populations, because hospitalizations in patients with CTD-ILD, patients with CHP, and patients with non-IPF IIP were associated with superior transplant-free survival compared with IPF. One of the major findings of the paper concerns the potentially harmful effects of immunosuppression in non-IPF ILDs. This result should be interpreted with caution, because this subgroup of patients included very different clinical entities for which the immunosuppressive treatment has been reported to be potentially effective (such as CTD-ILD) or harmful (such as idiopathic IIPs). Another point that needs to be clarified is the effect of antifibrotic treatment on hospitalizations. In patients with IPF, antifibrotics could be effective in reducing the events related to disease progression,

Originally Published in Press as DOI: 10.1164/rccm.202401-0203ED on February 28, 2024

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.

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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