





## Lung transplant in familial pulmonary fibrosis: the road ahead

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Pulmonary fibrosis (PF) is the most common indication for lung transplantation, with the proportion of adult lung transplants performed for interstitial lung disease (ILD) increasing from 38% to 47% over the past decade.<sup>(1)</sup> Although transplant improves survival of carefully selected patients with PF, recipients tend to have worse outcomes and lower life expectancy than those with other indications.<sup>(2)</sup> Chronic lung allograft dysfunction (CLAD) is responsible for most of the morbidity and mortality after the first year of transplantation. Approximately 20% of PF cases cluster in families—termed familial PF (FPF)—and, of these, up to one-third have a mutation in a telomere-related gene and/or shortened telomeres in addition to variants in other genes, such as those for surfactant proteins and mucin 5B.<sup>(3,4)</sup>

In this issue of the *Jornal Brasileiro de Pneumologia*, Bennett et al.<sup>(5)</sup> report the results of a single-center, retrospective cohort study assessing short- and long-term outcomes of patients with FPF in comparison with those with sporadic PF. The authors identified 9 patients with FPF and 74 with PF from a sample of 160 consecutive patients who underwent lung transplant at their institution in Siena, Italy. Their main conclusion was that there was no statistical difference between groups in CLAD-free and overall survival. Although patients with FPF were more likely to receive bilateral lung transplantation and differed from PF recipients by the choice of induction/maintenance immunosuppression that they received, this conclusion remained valid even after adjustment for these potential covariates. There was also no statistical difference observed in many secondary post-operative outcomes reported, including primary graft dysfunction or acute cellular rejection. Interestingly, patients with FPF were more likely to have lower pre-transplant hemoglobin and hematocrit levels that reemerged 180 days after transplantation. These analyses, as limited as they are by the small sample size, are important to initiate discussions regarding lung transplantation in FPF and, more broadly, in PF associated with genetic variants.

In the study by Bennett et al.,<sup>(5)</sup> only one-third of the patients with FPF and none of those with sporadic PF had genetic analyses available. Of the available data in FPF patients, none had variations in genes for surfactant proteins C/A2 and ABCA2 or for telomerase enzyme-related genes *TERT* and *TERC*; however, assessment of other important telomere-related mutations was unavailable (e.g., *PARN*, *RTEL1*, and *NAF1*). It is also critical to note that telomere length was not assessed in any of the patients. Despite the lack of genetic data, there are numerous clues that patients in the FPF cohort may have had an underlying telomeropathy. Notably, patients with

FPF were more likely to be anemic before surgery and 180 days after surgery, and the majority of those who were anemic were more likely to have macrocytosis.

Mutations in genes that encode proteins involved in telomere maintenance, as well as short telomeres in general, have been implicated in an array of ILDs. In patients with idiopathic pulmonary fibrosis (IPF), multiple mutations in telomere-related genes have been associated with familial IPF in addition to a smaller subset of patients with sporadic disease.<sup>(3,4)</sup> Furthermore, 25% of patients with sporadic IPF and 37% of those with familial IPF have telomere lengths shorter than the tenth percentile corrected for age, the former occurring even in patients without a known telomere-shortening mutation.<sup>(3)</sup> Although IPF has the best characterized association, telomeropathies are not limited to this ILD subtype and have been associated with patients with chronic hypersensitivity pneumonitis, nonspecific interstitial pneumonia, unclassifiable PF, and pleuroparenchymal fibroelastosis, among others.<sup>(6,7)</sup> The presence of short telomeres, regardless of the histological subtype, is associated with a rapid decline in lung function<sup>(7)</sup>; therefore, discussion of telomere dysfunction solely in the context of FPF alone may underestimate its impact on progressive fibrosing ILDs, which are the ILD subtypes most likely to require lung transplantation. Moreover, the true prevalence of FPF may be underestimated, because recent evidence suggests that up to one in six family members of patients with sporadic PF have unrecognized ILD.<sup>(8)</sup> These findings provoke the following considerations: should we be performing genetic testing in patients with FPF before transplant? Should we be assessing telomere length regardless of the underlying genetic mutation in order to better risk-stratify patients after transplantation?

Short telomere and/or telomere-related mutations have been associated with higher rates of complications after lung transplantation that extend beyond allograft dysfunction. These include bone marrow suppression, intolerance of immunosuppression, and renal insufficiency.<sup>(9-11)</sup> With regards to the allograft, short telomeres and telomerase complex mutations have been attributed to higher rates of and more severe primary graft dysfunction, shorter time to the onset of CLAD, and worse post-transplant survival.<sup>(12,13)</sup> Given the significant evidence that telomeropathies affect both pre- and post-transplant outcomes, should we be screening all patients with PF for short telomeres as part of their pre-transplant evaluation? Some transplant centers have proposed protocols to improve outcomes in these patients that include screening of candidates whose evaluation suggests manifestations of shortened telomeres (early graying, cytopenias or macrocytosis, liver

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dysfunction, family history of ILD).<sup>(6)</sup> The identification of short telomeres would invite more scrutiny regarding pre-transplant evaluation of the bone marrow and the liver to exclude other manifestations of short telomeres and, more importantly, to mitigate potential post-transplant complications. In the post-transplant period, the preemptive identification of short telomeres could lead to modification of immunosuppression, antiviral prophylaxis, and other potential drugs that could lead to bone marrow toxicity.

In summary, perhaps the most important implications of the study by Bennett et al.<sup>(5)</sup> do not lie in the conclusions made but in the uncertainties its limitations expose surrounding the pre- and post-transplant evaluation and the management of patients with PF with regards to telomerase dysfunction and telomere

length, regardless of their family history. Given the available evidence, it is possible that the overall survival benefit observed in patients with PF who receive a transplant is abrogated in those with short telomeres. Further studies are needed to assess the impact of routine assessment of telomere length in transplant candidates on post-operative care and transplant outcomes in order to develop evidence-based guidelines. Survival after lung transplant lags behind other solid organ transplants; ushering in the era of personalized medicine could lead to improved outcomes.

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