Lung transplantation outcome in adult surfactant-related interstitial lung disease: first evidence to move on

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A new study reports the first evidence to "move on" with lung transplantation in adult surfactant-related fibrotic ILDs. It highlights the need for better genetic characterisation of transplant candidates and cancer screening for these patients. https://bit.ly/3QxG73Z

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Interstitial lung disease (ILD) associated with genetic disorders of the surfactant system represents the rarest of the two cardinal causes of monogenic pulmonary fibrosis (2–8%), next to telomere-related gene (*TRG*) mutation-associated ILD (30%) [1]. Lung disease relates to pathogenic mutations of surfactant-related genes (*SRG*) such as those encoding for surfactant proteins C, A1 and A2 (*SFTPC*, *SFTPA1* and *SFTPA2*), the ATP-binding cassette subfamily A, member 3 protein (*ABCA3*), the thyroid transcription factor-1 (*NKX2-1*) and, as recently reported, surfactant protein B (*SFTPB*) [2, 3]. Dependent on the specific *SRG* mutations and additional modifiers, a great heterogeneity of phenotypes may result, including lethal neonatal respiratory distress syndrome, childhood ILD, adult progressive pulmonary fibrosis (PPF) and lung cancer [2]. There is evidence that *SRG* mutations lead to the development of PPF through impairment of trafficking and accumulation of the mutated proteins (*SFTPC*, *SFTPA2* and *SFTPA1*) and/or disruption of surfactant homeostasis *via* dysfunctional lamellar bodies in alveolar epithelial type 2 cells (*ABCA3* and *NKX2-1*) [4–9]. ILD, initially described in infants and children, is increasingly encountered in adults either in survivors from childhood or in patients developing adult-onset ILD, necessitating appropriate management [2]. So far, two randomised trials have been published, examining the roles of hydroxychloroquine or nintedanib in children, and failing to show substantial therapeutic effects [10, 11]. That said, to date, no proven effective pharmacological treatment exists. Besides the lack of specific trials for adult *SRG* mutation-associated ILD patients, the European Respiratory Society statement on familial pulmonary fibrosis states "In advanced disease, evidence shows that patients with monogenic pulmonary fibrosis may benefit from lung transplantation, when appropriate". They further note that because lung cancer has been documented in up to 37% of *SFTPA1*/*SFTPA2* mutation carriers, early referral and bilateral transplantation should be considered [12].

In the current issue of *ERJ Open Research*, Bermudez *et al.* [13] present the results of a pioneer work regarding lung transplantation (LTx) in adults with PPF associated with genetic disorders of the surfactant system. This retrospective, observational, multicentre study reports the outcome of carriers of *SRG* mutations transplanted in the French network between 1997 and 2018. Of 32 patients identified, only 20 were deemed to carry pathogenic or likely pathogenic mutations and included in the analysis. The median (interquartile range) age at diagnosis was 45 (40–48) years and at LTx was 51 (45–54) years. Two patients with *SFTPA1* mutations had a history of cured lung cancer before LTx. Bilateral LTx was the procedure of choice for 85% of patients and 30% required a high-emergency procedure. Regular immunosuppressive therapeutic protocols post-LTx were applied and the median survival was 8.6 years. Four patients developed chronic lung allograft dysfunction (CLAD)-bronchiolitis obliterans syndrome and two CLAD-restrictive allograft syndrome. Six patients without previous history developed cancer of the lung, skin, bladder and uterus.

As also indicated by Bermudez *et al*. [13], when interpreting these data, caution is necessary due to the design of the study. This concerns 1) the non-systematic selection of patients for the genetic analysis and their reporting as a group, and 2) the lack of a proper comparison cohort, making all conclusions related the overall survival of this patient group and the frequencies of side-effects rather unreliable.

Regarding the genetic analysis, this was left to the discretion of the different transplant teams responsible for the patients and recommended for subjects with start of symptoms at age <50 years. Whereas it is often difficult to define symptom onset retrospectively, more importantly it is not clear what fraction of all transplanted patients was analysed and in particular for which of the relevant genes. This completely precludes estimates of frequencies and the spectrum of *SRG* mutations in this transplant population. In addition, variants of unknown significance (VUS) were not included in the study [14]. The entire group of *ABCA3* patients of the cohort were *VUS* carriers, depriving us of relevant information about the post-LTx behaviour of those patients who are increasingly recognised in adulthood [8, 15]. In particular, for genes like *ABCA3* with several hundreds of variants, many are rare and private, so the likelihood increases of discovering novel disease associations; thus, it is important to report the individual variants suspected, for future association with the clinical conditions observed. Such tabulated information will allow reduction of the number of VUS, in conjunction with functional studies [16].

Regarding the outcome of the study participants, a key finding is that adult patients with ILD related to *SFTPA1*, *SFTPA2* and *SFTPC* mutations had an overall excellent survival post-LTx compared with currently available data from other recipients with ILD, both sporadic and inheritable. Unfortunately, the survival of the most relevant comparison group, *i.e.* all patients with ILD transplanted in France during the same time period, was not reported. In addition, a period effect, *i.e.* selection of the most recent patients for the relatively novel genetic analysis, and thus the selection of a cohort transplanted with more experience in the centres, was favoured by the study design. With these constraints in mind, we must consider all survival and frequency observations made. Indeed, in idiopathic pulmonary fibrosis (IPF), which represents worldwide the most common indication for LTx, the median post-transplant survival reported is 5.2 years for IPF and 6.7 years for other fibrotic ILDs [17, 18]. The present study results (median survival 8.6 years) are encouraging when compared with the survival post-LTx (median 3.75 years) of *TRG* mutation carriers reported by Phillips-Houlbracq *et al*. [19], a finding that probably relates to the fact that *SRG* mutation carriers were even younger with fewer comorbidities. Although none of the five patients with *SFTPA1* mutations died, in contrast to *SFTPA2* and *SFTPC* mutation carriers where 42.9% and 62.5% died, respectively [13], the numbers are too small to conclude that there are differences between the *SRG* mutations. There are two other retrospective single-centre LTx studies including patients with ILD due to *SRG* mutations. These are studies in infants and children, dealing with *ABCA3*, *SFTPB*, *SFTPC* and *NKX2-1* mutations [20] and *SRG* and other rare genes (*e.g. TBX4* and *FOXF1*) associated with ILD [21]. In the older study, whereas mortality of children was comparable to that in adults (overall 5-year survival of 79%), infants had a less favourable course (56%) [20]. In the more recent study, 8-year patient survival was 87% (75–99%) for children <12 years and 69% (55–83%) for those ⩾12 years old [21].

The other important consideration highlighted in the study by Bermudez *et al*. [13] is the frequency of side-effects, *i.e.* the association of lung cancer and other cancers with LTx in *SRG* mutation carriers with ILD, both before and after the procedure, given the increased risk of lung cancer development in IPF patients (10.2%) [22]. Based on the International Society for Heart and Lung Transplantation (ISHLT) guidelines for the selection of LTx candidates, recent malignancy (with a high likelihood of re-occurrence) is included in the risk factors for poor post-transplant outcomes and, as such, regular cancer screening should be performed prior to transplant [23].

ILD carriers of *SFTPA1* or *SFTPA2* mutations present an even higher risk, especially for adenocarcinoma (37%) [2]. The two *SFTPA1* patients with a history of localised lung cancer in the 5 years preceding LTx that were included in the study by Bermudez *et al*. [13] survived and presented no recurrence, questioning whether 5-year cancer-free survival is always necessary [24, 25]. Regular screening could lead to early diagnosis and effective treatment.

Equally vigilant should be the post-LTx screening for any cancer, since cancers (including lung cancer) represent the second most common cause of late deaths after LTx [26]. No haematological neoplasms were described in this cohort; however, two patients died of *de novo* development of lung cancer, one a *SFTPA2* and the other a *SFTPC* carrier, a percentage relatively higher than expected, and another four developed a variety of other cancers. The oncogenic effects of immunosuppressive treatment post-LTx are well recognised [26]. Given the association of *SFTPA1* and *SFTPA2* with an increased risk for lung cancer *per se*,

bilateral LTx should be prioritised and, in cases where this is not an option, tailoring of immunosuppressive regimens might be considered, as well as close lung cancer screening with at least an annual computed tomography scan as suggested by Bermudez *et al*. [13]. Although currently lacking sufficient data, it is important to investigate an adaptation of the immunosuppressive regimen post-LTx in patients carrying genetic variants associated with a higher risk of malignancy, as adopted in *TRG* carriers [19].

The results of the work by Bermudez *et al*. [13] on adult patients carrying *SRG* mutations, suggesting promising outcomes after LTx but a high incidence of cancers post-LTx, should be interpreted with caution due to the study being of retrospective design, lacking controls and having only a moderate number of patients. Importantly, early genetic diagnosis for rare variants causing ILD may help in prospectively stratifying LTx cohorts. Among the scientific community, great expectations for the future are the standardisation of the indications of genetic analysis, the enrolment of all *SRG* carriers in international registries, and the development of new pharmacological and gene-based therapies that could successfully restore dysfunction [27–30]. Until then, LTx remains the only "life-saving procedure" for those patients.

The present study contributes the first evidence to "move on" with LTx because of the validity of this option, and highlights the need for better strategies to minimise risk, in order to maximise outcomes, in patients with ILD associated with genetic disorders of the surfactant system.

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