Navigating the Road to Transplant in Pulmonary Arterial Hypertension: A Road Less Taken

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Dramatic advances in therapy for pulmonary arterial hypertension (PAH) in the last 20 years have improved survival from a median of 2.5 years in the pretreatment era to 7.5 years currently. However, impressive as that may seem, it is important to note that a median survival of 7.5 years is equivalent to that of surgically resected non-small cell lung cancer, thus underscoring the importance of lung transplantation as a treatment option in patients with PAH. In this edition of *Advances*, Edelman has reviewed the pathway to transplantation for patients with PAH, detailing the recommendations for timing of referral, listing for lung transplantation, the role of the lung allocation score in allocating a donor organ, and the outcome of lung transplantation.

The lung allocation score (LAS) was developed and implemented in May 2005.[1] Prior to that, lungs for transplant were allocated largely based on time on the waiting list; such a system is an obvious disadvantage for patients with rapidly progressive or unpredictably progressive disease. Parameters used to assess disease severity (risk of death without a transplant) were tailored to the majority of patients awaiting lung transplantation, individuals who had some form of parenchymal lung disease (idiopathic pulmonary fibrosis [IPF] [United Network for Organ Sharing (UNOS) Group D], cystic fibrosis [Group C], chronic obstructive pulmonary disease [COPD] [Group A]). It was soon recognized that the success of the LAS in optimizing utilization of organs for those who would most benefit excluded patients with pulmonary arterial hypertension (PAH). Analysis of patients in REVEAL (the Registry to Evaluate Early and Long-term PAH Disease Management) identified risk factors predictive of mortality in patients with PAH (functional class III/IV, impaired renal function, elevated b-type natriuretic peptide, reduced 6-minute walk distance [6MWD], elevated right atrial pressure [RAP], presence of a pericardial effusion, reduction in diffusion lung capacity for carbon monoxide). Unfortunately, the LAS did not reflect these risks for mortality. Another analysis from REVEAL in 2010 (5 years after introduction of the initial LAS) concluded that the LAS overestimated survival for patients who met criteria for listing for lung transplantation.[2] The observed 1-year mortality exceeded that predicted by LAS in 2 subgroups of patients: those with mean RAP $\geq$14 mm Hg (14.8%$\pm$1.9% vs 12.2%) and those with a 6MWD $\leq$300 m (17.3%$\pm$1.7% vs 14.8%).

After reviewing these and other data, UNOS and the Organ Procurement Transplant Network (OPTN) permitted the ability to grant exceptions to patients with PAH based on severely reduced cardiac index and signs of right heart failure (elevated RAP $\geq$15 mm Hg). Additional indicators of hemodynamic compromise of other organs (rising bilirubin and increasing creatinine) have recently been added to the LAS rating. According to OPTN, these additions ". . .will further improve the survival prediction for all diagnostic groups; these effects will likely be most impactful for candidates in diagnosis Group B (PAH/pulmonary hypertension)."[3] The effect of these revisions to the LAS will be analyzed in 3-5 years.

PAH is a rare disease and should represent a small proportion of patients undergoing lung transplantation. However, this disease affects a younger patient population than patients in Groups D and A, and the mean duration from diagnosis to death is second only to IPF (Group D). The LAS has improved organ utilization and coincided with an overall increase in the number of lung transplants per year. Yet, both the number and the percentage of those patients on the wait-list with a diagnosis of PAH have dropped steadily from 15.2% in 2004 (n=579), to 11% in 2008 (n=218), to 6.2% in 2013 (n=99). The percent of patients with PAH actually transplanted in 2013 (3.8%, OPTN; n=73) was less than the number of patients who were retransplanted (4.1%; n=79). Frankly, there is something seriously wrong with this.

Patients with PAH endure the longest time on the waiting list. Median wait time for candidates first listed in 2013 was 4.0 months: the shortest time was for COPD patients (2.6 months) and the longest time for PAH patients (9.7 months). PAH patients have the second highest mortality on the waiting list (second to group D patients with pulmonary fibrosis, who receive 54% of all lung transplants) (Figure 1).

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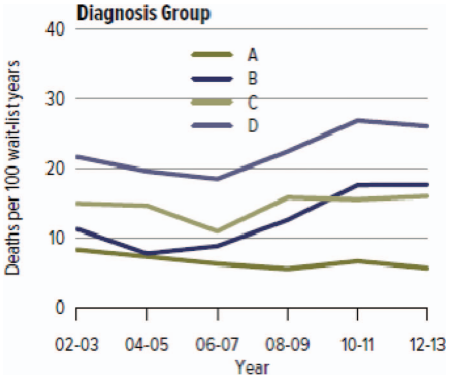

Figure 1: Pretransplant mortality among candidates aged 12 or older wait-listed for lung transplant. Patients with the highest mortality are those with IPF; second highest are patients with PAH.

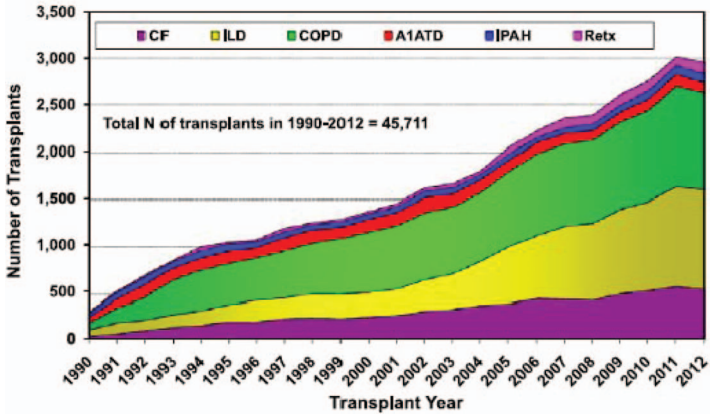

Figure 2: Adult lung transplantation according to indication and year of transplantation (transplants: 1990 to 2012). CF=cystic fibrosis–associated bronchiectasis; ILD=interstitial lung disease, which includes idiopathic pulmonary fibrosis (IPF); COPD=chronic obstructive pulmonary disease not associated with α_1-antitrypsin deficiency (A1ATD); A1ATD=COPD associated with A1ATD; IPAH=idiopathic pulmonary arterial hypertension; Retx=retransplantation.

A comparison of the likelihood of transplantation, death on the waiting list, and survival on the waiting list for PAH patients before and after implementation of the original LAS concluded that PAH patients were doing better since more patients were being transplanted by 5 years and fewer were dying on the transplant list (Figure 2). However, this does not consider the difficulty in obtaining wait-list status for these patients. In actuality, "better" is still not good! In this same study, only 42% of the wait-listed PAH patients were transplanted compared to 63% of all patients listed for lung transplant (28,183 listed and 17,687 transplanted).[4]

The perception of many PAH doctors, supported by currently available data, is that this generously donated resource is still not going to those most in need—by volume or disease severity.

PAH physicians remain optimistic that recent changes implemented by UNOS/OPTN, innovations in donor optimization (eg, ex vivo lung perfusion), and organ retrieval following cardiac death may benefit patients when disease modification or mitigation fails. In the future, transgenic organ transplants and autotransplants utilizing 3-dimensional printer scaffolding may become available and help to remedy this enduring problem for PAH patients.

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