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Survival and outcomes after lung transplantation for non-scleroderma connective tissue–related interstitial lung disease

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BACKGROUND: Patients with non-scleroderma connective tissue–related lung disease (NS-CTLD), including rheumatoid arthritis, idiopathic inflammatory myopathies, Sjögren syndrome, mixed connective tissue disease, and systemic lupus erythematosus, may be at risk for worse outcomes after lung transplantation because of immune dysregulation or extrapulmonary manifestations of their underlying disease. We compared survival, acute and chronic rejection, and extrapulmonary organ dysfunction after transplantation in patients with NS-CTLD and idiopathic pulmonary fibrosis (IPF).

METHODS: This was a retrospective cohort study of patients with NS-CTLD and IPF who were listed in the Scientific Registry of Transplant Recipients and underwent lung transplantation from May 5, 2005, to March 1, 2016.

RESULTS: Patients with NS-CTLD ($n = 275$) were younger, a higher percentage female and non-white than patients with IPF ($n = 6{,}346$). NS-CTLD patients did not have worse adjusted survival (hazard ratio, 1.14, 95% confidence interval [CI], 0.92–1.42; $p = 0.24$). They were not more likely to have an episode of acute cellular rejection (odds ratio, 0.96; 95% CI, 0.72–1.28; $p = 0.77$) or to develop bronchiolitis obliterans syndrome (odds ratio, 0.82; 95% CI, 0.60–1.12; $p = 0.21$). Patients with NS-CTLD were not more likely to require plasmapheresis or dialysis or to develop a lymphoproliferative malignancy or liver disease after transplantation.

CONCLUSIONS: We found no significant differences in survival, acute or chronic rejection, or extrapulmonary organ dysfunction in patients who underwent lung transplantation for NS-CTLD compared with IPF. In appropriately selected candidates, NS-CTLD should not be considered a contraindication to lung transplantation.

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Respiratory failure is a significant source of morbidity and mortality in patients with connective tissue disease, including scleroderma, mixed connective tissue disease (MCTD), polymyositis, dermatomyositis, systemic lupus erythematosus (SLE), Sjögren syndrome, rheumatoid arthritis, and anti-synthetase syndrome.[1] Lung transplant may be considered in patients with connective tissue–related interstitial lung disease (CTLD) who progress despite appropriate immunosuppression. Scleroderma accounts for

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most CTLD lung transplants in the United States, and there is growing evidence that carefully selected candidates with scleroderma-related pulmonary fibrosis have similar short-term and long-term survival compared with patients with non-scleroderma interstitial lung disease.[2,3] However, significantly fewer lung transplants are performed in patients with non-scleroderma (NS-CTLD).[4,5] This is partly because of lack of data on survival and allograft function in the NS-CTLD population and concern for extrapulmonary manifestations of the underlying connective tissue disease after transplant.[6]

The only previous large-scale study of lung transplant in CTLD found that CTLD patients had worse survival but lower rates of acute rejection than patients with chronic obstructive pulmonary disease and similar survival and acute rejection rates as patients with idiopathic pulmonary fibrosis (IPF).[7] The authors, however, did not differentiate between patients with scleroderma-CTLD and NS-CTLD in their survival analysis or exclude patients with NS-CTLD who underwent transplant for pulmonary hypertension without parenchymal lung disease. In addition, they did not control for potential confounders of survival such as age, bilateral vs single lung transplant, or severity of illness.

Previous studies of CTLD and lung transplant have not investigated pre-transplant sensitization among patients with NS-CTLD. Given the underlying immune dysregulation in this population, NS-CTLD patients may be at risk for being highly sensitized before transplant and for developing antibody-mediated rejection and subsequent chronic lung allograft dysfunction. For example, patients with autoimmune-related renal failure are more likely to be sensitized and to have graft loss as a result of rejection.[8] Independently of allosensitization, B-cell and T-cell dysregulation in NS-CTLD may also affect post-transplant outcomes. For example, patients with SLE and Sjögren syndrome have higher levels of B-cell activating factor, which is associated with increased risk for antibody-mediated rejection after renal transplant.[9]

Finally, although several single-center studies have reported the respiratory course of patients with connective tissue disease after lung transplant, no large-scale studies have been conducted of extra-pulmonary organ dysfunction in NS-CTLD patients who have received transplants.[10,11] These data are important because patients with NS-CTLD are at increased risk for extrapulmonary manifestations of their diseases, such as kidney failure and venous thromboembolism in SLE, autoimmune liver disease in MCTD, and Sjögren syndrome or lymphoproliferative disorders in rheumatoid arthritis.[12]

The primary objective of this study was to evaluate whether there is a difference in survival, allograft function, or extrapulmonary organ dysfunction after lung transplant in patients with NS-CTLD compared with patients with IPF. The secondary objective was to evaluate whether there is a difference in allosensitization between patients with NS-CTLD and patients with IPF who undergo lung transplant. Our hypotheses were that compared with patients with IPF, patients with NS-CTLD would have similar survival but increased allograft and extrapulmonary organ dysfunction after lung transplant.

Methods

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donors, candidates on the waiting list, and transplant recipients in the United States submitted by the members of the Organ Procurement and Transplantation Network. The United States Department of Health and Human Services Health Resources and Services Administration provides oversight to the activities of the Organ Procurement Transport Network and SRTR contractors. This was a retrospective cohort study of all patients listed in the SRTR who underwent lung transplant from May 5, 2005 (the beginning of the lung allocation score era), through March 1, 2016. We excluded patients who received combined organ transplants, including heart-lung. The Brigham and Women's Hospital Institutional Review Board deemed formal review of this study unnecessary.

We used diagnosis codes and descriptive text codes to identify patients who received transplants for NS-CTLD, including rheumatoid arthritis, polymyositis, MCTD, Sjögren syndrome, SLE, dermatomyositis, autoimmune lung disease not otherwise specified, Wegner disease with fibrosis, and anti-synthetase syndrome. To eliminate patients whose lung transplant was primarily for autoimmune-related pulmonary hypertension rather than interstitial lung disease, we excluded patients with a percentage predicted forced expiratory volume in 1 second (FEV_1) $>$ 70%, a percentage predicted forced vital capacity (FVC) $>$ 70%, and a mean pulmonary artery pressure (mPAP) $>$ 25 mm Hg, or a percentage predicted FEV_1 $>$ 70% and a percentage predicted FVC $>$ 70% with an unknown mPAP. We also used the diagnosis code for IPF to identify all patients with a diagnosis of IPF.

Clinical, sociodemographic, and allosensitization variables

For each patient, we collected, where available, age, sex, race (white or non-white, including Latino), percentage predicted FVC, 6-minute walk test distance, history of pre-transplant malignancy, pulmonary embolism, chronic steroid use, pre-transplant mPAP, pre-transplant creatinine, need for mechanical ventilation or extracorporeal membrane oxygenation (ECMO) before transplant, and procedure type (single or bilateral/double). We also collected data on the percentage reactivity on the pre-transplant peak panel reactive antibody (PRA) screen and whether class I or class II human leukocyte antigen (HLA) antibodies were ever present pre-transplant. We recorded, where available, whether a prospective crossmatch was performed before transplant and whether an auto-crossmatch was ever positive. Finally, we collected data on the use of plasmapheresis during the initial hospitalization and subsequent follow-up.

Outcomes

For each patient, we calculated time to death, retransplant, or last status update (if alive). We collected data on additional allograft outcomes, where available, including development of acute rejection and bronchiolitis obliterans syndrome (BOS). We collected data on extrapulmonary organ function outcomes,