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Survival after lung transplantation in systemic sclerosis. A systematic review

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Summary
Background: Lung transplantation is a life-saving option for systemic sclerosis (SSc)-associated pulmonary arterial hypertension (PAH) and interstitial lung disease (SSc-ILD) patients. However, some programs may be concerned about the possibility of excess post-transplantation mortality related to the extra-pulmonary manifestations of SSc. The objective of this study was to evaluate survival of SSc patients post-lung transplantation. We secondarily evaluated SSc lung transplant recipient characteristics (age, sex, and type of SSc lung disease), and discussed post-lung transplantation survival of SSc patients and non-SSc patients (idiopathic PAH, and ILD).
Methods: A systematic review of MEDLINE, EMBASE, Cochrane Central Registry of Controlled Trials and CINAHL (all inception to 2012) was performed to identify studies evaluating post-lung transplant survival in SSc compared to PAH and ILD patients. Two reviewers independently abstracted study and survival data.
Results: Two hundred twenty-six citations were screened to identify 7 observational studies reporting SSc patients who underwent single lung, double lung, or heart-lung transplantation. Mean age at transplantation ranged 46–53 years. SSc post-transplantation survival ranged 69%

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—91% at 30-days, 69%—85% at 6-months, 59%—93% at 1-year, 49%—80% at 2-years, and 46%—79% at 3-years. Causes of death included graft failure, infection, cardiac events, hemorrhagic stroke, respiratory failure, malignancy, pulmonary hypertension, complications of bronchiolitis obliterans syndrome, anesthetic complication, and scleroderma renal crisis. There were no reports of recurrence of SSc in the lung allograft.
Conclusion: The short-term and intermediate-term survival post-lung transplantation are similar to IPAH and ILD patients requiring lung transplantation.

Introduction

Systemic sclerosis (SSc, scleroderma) is a disease characterized by immune activation and inflammation that leads to vasculopathy and fibrosis. It can affect the skin, blood vessels, and internal organs. The internal organs most commonly affected are kidney, gastrointestinal tract, and lung. Over the past decade, the use of angiotensin-converting enzyme inhibitors has greatly reduced the burden of renal complications, making lung disease the leading cause of morbidity and mortality in SSc patients [1]. The two principal manifestations of SSc lung disease are pulmonary arterial hypertension (PAH) and interstitial lung disease (ILD) [2].

PAH is a lethal disease characterized by elevated pulmonary artery pressure that leads to dyspnea, heart failure, and death. In the setting of SSc, the prevalence of PAH ranges from 5% to 12% [3—5], and is a leading cause of death [6,7]. Historically, SSc-PAH had a median survival of 12 months [6]. In the modern treatment era, the median survival has improved to 3—4.9 years [5,8,9]. Similarly, idiopathic pulmonary arterial hypertension (IPAH) historically has a median survival of 2.8 years [10]. In the modern treatment era, 3-year survival has improved to 76%—85% [9,11,12]. The use of PAH-specific therapies (endothelin receptor antagonists, phosphodiesterase 5 inhibitors and prostaglandin analogues) used alone or in combination, has resulted in improvements in six-minute walk distance, functional class, cardiac hemodynamics, quality of life and time to clinical worsening [13]. Yet none of these treatments are curative.

ILD also portends a poor prognosis, with mean survival of 2—5 years from the time of diagnosis [14]. Estimated mortality rates are 64.3 deaths per million men and 58.4 deaths per million women [15]. Prognostic factors for survival in SSc-PAH, SSc-ILD and IPAH include baseline mean pulmonary artery pressure, sex, functional class and signs of right heart failure [16].

Lung transplantation is performed to prolong survival and to improve the quality of life for patients with end stage lung disease [17]. Nearly three decades have passed since the procedure was first introduced, and this extended experience has led to improvements in outcomes for lung transplant recipients. Despite the recent increase in the number of patients undergoing lung transplantation over the past decade, patients with systemic autoimmune rheumatic disease, such as SSc, are often denied transplantation because of concerns about the short- and long-term outcomes [18].

However, very little is known about the survival of SSc patients, who undergo lung transplantation. The objective of this study was to evaluate survival of SSc patients' post-lung transplantation through a systematic review of the literature. We secondarily evaluated SSc lung transplant recipient characteristics such as age, sex and SSc lung disease type, and discussed post-lung transplantation survival of non-SSc patients (idiopathic PAH, and ILD).

Methods

Data sources and searches

An investigator (IYK) and an information specialist from the University Health Network library services independently performed the literature search. Studies were identified using Ovid MEDLINE (1986—2012), EMBASE (inception to January 2012) Cochrane Central Registry of Controlled Trials (inception to 2012) and CINAHL (inception to 2012). The following keywords, alone or in combination, with mapping of term to subject heading were used in the database search: "scleroderma", "systemic sclerosis", "lung transplantation", "pulmonary fibrosis", and "pulmonary hypertension". No language, publication date or publication status restrictions were imposed. The results of the 2 independent searches were compared to ensure completeness.

Study selection

Titles and abstracts were screened to identify studies reporting survival post-lung transplantation in SSc patients. Studies were included if they reported 1) human SSc patients (classified as SSc using the American College of Rheumatology classification criteria [19], or physician-based diagnosis), 2) lung transplantation (single lung, double lung or heart lung transplantation), and 3) reported survival as an outcome. The primary outcome for this study was death from all causes. Studies were ineligible if they included 1) only individuals aged <16 years, 2) lung transplantation for indications other than SSc-PAH or SSc-ILD, 3) patients with another rheumatic disease (rheumatoid arthritis, systemic lupus erythematosus, mixed connective tissue disease), or 4) were animal studies. The reference lists of selected articles were hand searched for relevant publications.

Data abstraction

Two reviewers (IYK, AK) independently abstracted data using standardized, pilot tested forms. The reviewers were