Editorial

Evidence for lung transplant in rapidly progressive interstitial lung disease: how to select patients most likely to benefit and future directions

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In the latest issue of *Shanghai Chest*, Benedetto and colleagues have presented "*Urgent lung transplant in acute pulmonary scleroderma*: *a case report*" describing the case of a patient with systemic scleroderma (SSc) and acute onset of respiratory failure who was successfully bridged to bilateral lung transplant (LTx) with awake veno-venous extracorporeal membrane oxygenation (VV ECMO) (1). This case report focused on the role of VV ECMO as a life-saving option in patients with refractory and rapidly progressive interstitial lung disease (RPILD) leading to end-stage respiratory failure.

In patients with connective tissue diseases (CTDs), pulmonary involvement in the form of either interstitial lung disease (ILD) or pulmonary hypertension (PH) remains a significant cause of morbidity and mortality (2). In view of the multisystem nature of CTDs, with concurrent gastrointestinal, cardiac and renal involvement, CTD-associated ILD (CTD-ILD) remains a relative contraindication for LTx as per recent International Society for Heart and Lung Transplantation (ISHLT) guidelines (3,4). This includes SSc, which is a multisystem autoimmune condition that primarily affects the young female population. This represents a group of otherwise good potential LTx candidates in terms of physical fitness and motivation, and previous studies have demonstrated that appropriately screened and carefully selected individuals have no difference in outcomes or allograft function (5,6). It is clear that LTx for CTD-ILD remains controversial given the recently published ISHLT data which highlighted that only 0.9% of LTx performed were related to CTD-ILD (3). The potential reasons for such low numbers are multifactorial and include concerns over survival and clinical outcomes, and the impact of extrapulmonary manifestations on the transplanted lungs. As a consequence, the first point we would like to highlight is that all patients diagnosed with a CTD-ILD should be considered for early and timely referral for LTx due to the high likelihood of extra-pulmonary manifestations that will require thorough investigation with both medical and surgical input. This was also recently highlighted in the updated 2021 ISHLT consensus document for the selection of LTx candidates (4).

Benedetto and colleagues have presented a case of

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RPILD, where the patient required VV ECMO and then went on to have LTx due to the lack of clinical improvement (1). In this case, the unifying diagnosis of SSc was made following an acute deterioration and hospital admission, the patient having first presented to rheumatologists two months earlier. We would therefore like to take this opportunity to summarise the current landscape within LTx and SSc. Specifically, SSc is an autoimmune disease characterised by microvascular damage and generalised fibrosis of organs (including skin, lung, renal, cardiac and gastrointestinal involvement), with multiple studies confirming a higher prevalence in women compared to men (7). However, the extrapulmonary manifestations can lead to absolute and relative contraindications to LTx (3), such as oesophageal abnormalities, renal dysfunction and a history of non-healing ulcers to highlight a few. For this reason, many transplant centres are reluctant to consider acutely and critically unwell patients who have not previously been reviewed and undergone full assessment of these extra-pulmonary manifestations, as the risk of a poor outcome would be deemed unacceptably high, risking poor organ utilisation. It would be interesting to understand which investigations of extra-pulmonary manifestations were undertaken and available in this case when the decision was made to list for LTx, although the gastrointestinal tract and kidneys are mentioned in the context of ruling out major organ involvement.

This case report also stimulates a discussion regarding current and emerging therapies in RPILD. At this point, it would be interesting to understand more in detail why the authors felt that the diagnosis was SSc, rather than anti-melanoma differentiation-associated gene 5 (MDA5) dermatomyositis (DM). The positivity of anti-MDA5 antibodies is strongly associated with RPILD in DM, with poor outcomes once this process begins (8). Although there is a significant crossover between DM and SSc, it is unclear from the history provided how the authors came to their diagnostic conclusion. There appears to be no macroscopic cutaneous features in this case, though the skin biopsy provided key diagnostic information and this may be why the patient was given the diagnosis of SSc. In all cases of RPILD, it is important to establish the cause, in order to investigate for associated features and guide treatments. Accepting the authors' diagnosis of SSc, our next comment is related to the initial immunosuppressive treatment. Ultimately, the mainstay of treatment in either diagnosis remains aggressive and early immunosuppression. In the context of a RPILD, it is standard practice in most centres for patients to receive pulses of intravenous (IV) methylprednisolone followed by further immunosuppressive therapies as well as more targeted treatments, such as PH therapies and anti-reflux treatments (9,10). The dose of IV methylprednisolone can be 500–1,000 mg/day for 3 days depending on risk factors and institutional practice, and we would be interested in the rationale behind the combined immunosuppression regime given in this case as first-line treatment.

Furthermore, VV ECMO is well established as a bridge to LTx (11-15) and as a bridge to recovery for severe acute respiratory failure. However, the recent coronavirus disease 2019 (COVID-19) pandemic has increasingly brought forward the concept of VV ECMO as a "bridge to decision" for those in critical respiratory failure but not yet known to a transplant team (16). Although these concepts have been already applied for several years, it is important to remember that VV ECMO in other situations can be a "bridge to nowhere" and leave medical teams and families distraught when support has to be switched off. In this specific case, immunosuppression was commenced once the diagnosis of SSc was confirmed. Despite this, the patient clinically deteriorated further requiring non-invasive ventilatory support. Due to complicating factors, including pneumothorax and pneumomediastinum, awake VV ECMO was given priority over invasive mechanical ventilation (MV), initially with the aim of bridging to recovery, but ultimately it became a successful bridging strategy to LTx. However, to date only a few retrospective analyses and case reports have described the use of ECMO as a bridge to emergency LTx in patients with life-threatening RPILD secondary to CTD unresponsive to conventional immunosuppressive treatment (17-20). In this highly-selected group of case reports, initial outcomes are excellent, but follow-up is only for one year or less, and so data on long-term outcomes remain lacking as identified by the authors themselves.

We applaud and would like to highlight the use of awake VV ECMO in this case, which is now a well-established practice, especially in those patients awaiting LTx, and increasingly as first-line treatment instead of intubation and MV to avoid the common intensive care unit (ITU)-related complications associated with, but not limited, to sedation (delirium and critical care weakness) and invasive MV (ventilator-associated lung injury) (21,22). This case provides an example of the benefit of access to awake VV ECMO given the complicating factors already highlighted.

Maintaining and ambulating patients on VV ECMO is challenging, and requires a highly trained and motivated workforce that cares for a volume of patients per annum on ECMO to maintain the skillset.

This challenge of managing resources brings us to our final discussion point. Many countries and healthcare programmes constantly have to strike a balance between patients who need LTx and those who will gain the greatest benefit from such a scarce resource, as well as concentrating highly specialised services such as ECMO into a handful of tertiary or quaternary cardiothoracic centres. Concerns remain that patients with CTD-ILD may be at risk of worse outcomes after LTx because of the extrapulmonary clinical features of their underlying disease. However, reports from high-volume transplant centres suggest similar posttransplant outcomes in patients with CTD-ILD, especially SSc, compared with patients with non-CTD-ILD and other common indications for LTx such as PH with the understanding that these patients with CTDs are carefully selected for transplant (23). Recent evidence on LTx and CTD-ILD is focused on SSc-associated ILD, though clinical significance remains low as it is mostly related to small case series or single case reports. In their single-centre retrospective cohort study, Chan and colleagues reported that patients undergoing bilateral LTx for scleroderma-related pulmonary disease have similar 1- and 5-year survival as those with restrictive lung disease (24). Another retrospective study particularly relevant to this case, given the diagnostic uncertainty between SSc and DM, is the analysis of the survival of patients transplanted for CTD-ILD conducted by Takagishi and colleagues, which found a reduced 1- and 3-year survival for those in the polymyositis and DM subgroup, though clinical phenotypes and antibody status were not identified (25). Finally, this case report provided only a 3-month follow-up despite the fact that the hospital stay was 3 months. Although other reports demonstrated that patients can survive several years (18). Still, there remains a significant paucity of published data on long-term outcomes in this patient group.

In conclusion, Benedetto and colleagues have provided an example of successful use of awake VV ECMO as a rescue therapeutic strategy of bridging to LTx in the context of a life-threatening RPILD secondary to CTD (1). Despite the medical complexity and risk of perioperative and postoperative complications in this context, this case report highlights that VV ECMO could be beneficial in a highly-selected patient cohort. The authors have highlighted this crucial point and we would strongly advocate for an international pooling of outcomes for all CTD-ILD patients undergoing LTx, but especially in cases of RPILD. Specifically, anti-MDA5 CTD-ILD is associated with a RPILD, DM, and poor response to immunosuppressive treatment. It would be reasonable to consider LTx referral early in these patients, assuming there are no significant extra-pulmonary manifestations. In addition, LTx centres should ensure they have the experience and skills to manage these complex patients. For this reason, we believe that prompt referral of these patients to specialized transplant centers and consideration for LTx are of paramount importance. In fact, one area in which several reports agree is that all patients with RPILD and without comorbidities should be urgently referred for consideration of LTx (1,17,18). Alongside this, further studies with longer follow-up and data on relapse rates are required.

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