Lung and heart-lung transplantation for systemic sclerosis patients. A monocentric experience of 13 patients, review of the literature and position paper of a multidisciplinary Working Group

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Pulmonary involvement (mainly pulmonary arterial hypertension [PAH] and interstitial lung disease [ILD]) is a frequent and severe complication of systemic sclerosis (SSc) [1,2]. In SSc, the prevalence of PAH is between 5 and 10% and the prevalence of ILD is around 40% [1,3–7]. Despite therapeutic advances, none of the treatments are curative and PAH and ILD are now the leading causes of death in patients with SSc [8].

Median survival for SSc patients and PAH is still only 3 to 4 years [9–11]. Pulmonary hypertension (PH) in SSc can be either isolated (PAH belonging to the group 1 of the classification of PH [12] or associated with ILD, belonging to the group 3), with a dismal prognosis and a poor treatment effect [10,11,13]. Moreover, pulmonary veno-occlusive disease (PVOD), belonging to the group 1 [12], appears as a non-rare cause of connective tissue diseases (and especially SSc)-related PH [14,15]. PVOD is usually associated with a poor prognosis and a high risk of pulmonary oedema during specific PAH treatment [16–20]. Recent guidelines state that patients with PVOD should be referred to a transplant centre for evaluation as soon as the diagnosis is established [12]. ILD generally progresses very slowly but some patients (<10%) develop severe chronic respiratory insufficiency [1]. The treatment options for ILD are quite limited and cannot systematically prevent disease progression [21]. Therefore, when treating SSc patients with ILD and/or PAH/PH, it is legitimate to consider whether it is appropriate to refer them for lung (LT) or heart-lung (HLT) transplantation, which can be a life-saving option and can improve the quality of life for patients with an advanced lung disease.

However, there is a certain reluctance to refer SSc patients for (H)LT, which could partly explain the small number of patients with SSc (or other connective tissue disease) to have received

**Summary**

Systemic sclerosis per se should not be considered as an a priori contraindication for a pre-transplantation assessment in patients with advanced interstitial lung disease and/or pulmonary hypertension. For lung or heart-lung transplantation, a multidisciplinary approach, adapting the pre-transplant assessment to systemic sclerosis and optimizing systemic sclerosis patient management before, during and after surgery should improved the short- and long-term prognosis. Indications and contraindications for transplantation have to be adapted to the specificities of systemic sclerosis. A special focus on the digestive tract involvement and its thorough evaluation are mandatory before transplantation in systemic sclerosis. As the oesophagus is almost always involved, isolated gastro-oesophageal reflux disease, pH metry and/or manometry abnormalities should not be a systematic per se contraindication for pre-transplantation assessment. Corticosteroids may be harmful in systemic sclerosis as they are associated with acute renal crisis. A low dose corticosteroids protocol for immunosuppression is therefore advisable in systemic sclerosis.
this type of treatment [22]. This reluctance is largely due to the systemic nature of the disease and the risk of specific peri- and postoperative complications including SSc renal crisis (SRC), digital ulcers (DU) sometimes leading to amputations, and increased risk of microaspiration due to gastro-oesophageal reflux disease (GERD) worsening [23,24]. Nevertheless, the results published on the long-term outcome of LT/HLT in SSc patients are quite encouraging, even if specific complications and increased mortality in the short postoperative period have been sometimes reported [23–28]. However, there are currently no official recommendations to guide clinicians with regard to contraindications and specific management requirements before, during and after LT/HLT in SSc patients. Based on a multidisciplinary approach, adapting the pre-transplant assessment to specific SSc contraindications and optimize SSc patient management before, during and after surgery should improved the short- and long-term prognosis. Therefore, a Working Group was set up, bringing together pneumologists, surgeons, intensive care unit physicians, cardiologists, gastroenterologists, radiologists, and SSc specialists. This Working Group reports a monocentric experience, reviews the literature, and discusses a number of issues on SSc patients. These issues include indications for transplantation, candidate selection and management before, during and after the transplantation. We additionally discuss anti-rejection treatment in the context of SSc multisystemic manifestations. However, it must be emphasized that these are not official recommendations but a position paper aiming at filling the gap and helping in the selection of SSc patients, which remains a case-by-case decision, and in managing patient, taking into account the specificity of SSc.

Methods

We used a three-step approach:

- we reviewed the files of all SSc patients who underwent LT or HLT in one center (Marie-Lannelongue Hospital, Le Plessis-Robinson, France) in order to describe our experience in managing these patients and identify the complications observed in these patients;
- we reviewed the literature on case reports and series of SSc patients undergoing LT or HLT. We search MEDLINE between January 1960 and January 2012 using the following relevant terms: (“Scleroderma, Systemic” OR “systemic sclerosis”) AND (“transplantation”);
- the Working Group (DL, LS, AB, JLP, EH, LM, OS, BL, MG, XJ, FS, PYH, NL, OV, LG, GS, OM, EF, PD, MH, SM) met twice and had 10 phone conferences addressing each issue raised by the analysis of our experience and the literature. The Working Group also addressed the indications for transplantation, candidate selection and management before, during and after the transplantation.

The manuscript was reviewed and approved by each member of the Working Group. Then, it was analysed and modified by an independent Reading Group including specialists having a special focus on rare lung diseases and connective tissue disease and a thorough experience in lung transplantation in this context (JLP, VC, DF, BW). Each member of the Working and Reading groups approved the final manuscript.

Monocentric experience of lung and heart-lung transplantation in patients with systemic sclerosis

Study design

We retrospectively reviewed data from all patients who underwent lung (n = 275) or heart-lung transplantation (n = 140) (LT/HLT) recipients between 1993 and 2012 at the Marie-Lannelongue Hospital, Le Plessis-Robinson, France and who fulfilled the American College of Rheumatology criteria for SSc or Leroy and Medsger’s classification criteria [29,30]. All patients were evaluated in accordance to the general practice established by guidelines for the selection of (H) LT candidates [31]. All patients were referred by expert centres for the management of SSc. PH was defined by right heart catheterization in accordance to recently updated ERS/ESC guidelines (mean pulmonary arterial pressure > 25 mmHg and pulmonary capillary wedge pressure < 15 mmHg) [12]. The diagnosis of ILD was established according to the underlying radiological pattern assessed by high resolution tomography of the chest (HRCT) as well as the clinical context and results of respiratory function tests [32,1]. PVOD was suggested in the presence of ≥ 2 of the following signs: centrilobular groundglass opacities, septal lines, and lymph node enlargement [3,14,16,17]. All relevant data, i.e. baseline characteristics including age, gender, type of SSc, postoperative complications, including acute and chronic rejection according to the International Society of Heart and Lung Transplantation (ISHLT) criteria [33,34] and the survival status of patients were retrospectively analyzed.

Results

Between 1993 and 2012, 415 LT or HLT were performed for end-stage lung and heart-lung disease. Among them, 13 patients (3.1%) fulfilled the American College of Rheumatology criteria for SSc or Leroy and Medsger’s classification criteria for SSc [29,30].

Baseline characteristics

The mean age of SSc patients at the time of transplantation was 48 ± 8 years. Eleven patients had limited SSc and two patient diffuse SSc. Three patients presented with a history of DU. None of these DUs were considered as active at the time of registration for (H) LT. No patient had chronic renal insufficiency.
Three patients had an isolated ILD, 8 an isolated PAH and 2 the combination of ILD and PH. All patients with PAH also presented clinical and radiological signs suggestive of PVOD [17,35]. One patient had associated left cardiac involvement. All the 4 patients with ILD were treated with long-term corticosteroids associated to other immunosuppressive treatments (cyclophosphamide or mycophenolate mofetil [MMF]). GERD was observed in all patients and considered severe in 5 patients by the physician. However, oesophageal mobility and gastric emptying were not systematically assessed in the patients before transplantation.

**Lung or heart-lung transplantation**

One patient underwent a single LT for ILD, 7 a double LT for isolated PAH in 4 cases, isolated ILD in 2 cases and association of PH and ILD in one case. Finally, 5 patients underwent a HLT for an isolated PAH in 4 cases and the association of PH and ILD in 1 case. HLT was indicated in PH patients regardless of ILD association with advanced heart disease (i.e. need of inotropic support, severe right heart dysfunction on echocardiography, major right heart enlargement, right atrial pressure (RAP) > 20 mmHg, increased bilirubin and renal failure) or presence of a SSc-related cardiac disease. The median waiting time for transplantation was 5.6 months (0–14 months). National priority listing was obtained in 5 patients waiting HLT (n = 2) or double LT (n = 3) in a context of imminent right heart failure. The median time of mechanic ventilation after transplantation was 11 days (ranging between 1 to 90 days). Vasopressive treatments were administered more than one day in 10 SSc patients. Extracorporeal Membrane Oxygenation (ECMO) was used in three patients after transplantation because of severe acute graft dysfunction.

**Early complications (within the first 3 months)**

The specific complications directly attributed to SSc were severe DU in three patients with necessity of amputation in one case and SRC in one patient (table I). Acute rejection was observed in 6/13 (46%) patients (10 episodes: 3 cases of humoral rejection, 5 cases of cellular rejection and 2 cases of diffuse alveolar damage). All these episodes were successfully treated according to the type of acute rejection. Two patients developed episodes of severe gastric stasis that were complicated by aspiration pneumonia. For these two patients, GERD was considered as severe before transplantation. Three patients (23%) died within the 3 months following lung transplantation from the following causes: primary graft failure, multi-organ dysfunction in the context of *Staphylococcus aureus* pneumoniae and acute cerebellar infarction.

**Late complications (after the first 3 months)**

Late complications included infectious complications (1 pleural tuberculosis, 2 bacterial pneumonia and 2 invasive pulmonary aspergillosis), 1 Kaposi sarcoma, 1 SRC leading to a chronic renal insufficiency 44 months after LT and 3 chronic rejects complicated by bronchiolitis obliterans syndrome (BOS).

**Survival**

The median time of follow-up was 7.3 months after transplantation (ranging between 3 days–133 months). Eight patients

<table>
<thead>
<tr>
<th>Type of complication</th>
<th>Number of episodes/number of patients</th>
<th>Mechanisms (number of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute reject</td>
<td>10/6</td>
<td>Humoral rejection (3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cellular rejection (5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diffuse alveolar damage (2)</td>
</tr>
<tr>
<td>Infectious complications</td>
<td>10/9</td>
<td>Bacterial pneumonia (8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Viral pneumonia (cytomegalovirus) (2)</td>
</tr>
<tr>
<td>Renal complications</td>
<td>4/4</td>
<td>Acute scleroderma renal crisis (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acute renal failure due to hemodynamic instability (3)</td>
</tr>
<tr>
<td>Gastrointestinal complications</td>
<td>2/2</td>
<td>Gastric stasis complicated by aspiration pneumonia (2)</td>
</tr>
<tr>
<td>Skin complications</td>
<td>3/3</td>
<td>Digital ulcers (amputation in one case) (3)</td>
</tr>
<tr>
<td>Neurological complications</td>
<td>1/1</td>
<td>Acute cerebellar infarction</td>
</tr>
<tr>
<td>Complications of suture</td>
<td>5/5</td>
<td>Scarpah dehiscence (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thoracotomy dehiscence (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aortic anastomosis rupture (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Right bronchial stenosis (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Right lateral tracheal fistula (1)</td>
</tr>
</tbody>
</table>
(62%) died during follow-up including 5 patients (38%) during the first year after transplantation. Overall survival rate was 59% at 3 yrs. Details about the causes of death are listed in Table II.

### Literature data on lung/heart-lung transplantation and systemic sclerosis

Data on LT/HLT in patients with SSc are scarce in the literature [23,24,26,27,36,37] and include 4 main studies [23,24,26,27]. A recent review is available [38]. Massad et al. reported 47 SSc (27 single LT and 20 double LT) patients based on data extracted from UNOS (United Network for Organ Sharing). In this series, there was no significant difference in mortality between the SSc patients and those transplanted for other conditions. Furthermore, the authors found no difference in terms of acute rejection during the first year post-LT and chronic rejection (11% in SSc patients vs 9% in other patients). In 2009, Shitrit et al. [27] combining their experience in 7 SSc patients who underwent single LT and the previous series reported by Massad et al. [26] found that bacterial infections and graft failure were the two leading causes of death after LT in SSc patients. The 2- and 5-year survival rates were 72% and 55%, respectively.

Schachna et al. reviewed the data on 29 SSc patients transplanted in the Johns Hopkins Hospital and the University of Pittsburgh Medical Center [23]. A clearance of < 50 mL/min, active cutaneous ulcers, severe cutaneous involvement of the thorax and severe gastro-oesophageal reflux that could not be controlled by medical therapy were considered as contraindications for LT in this study. The control group consisted of patients with idiopathic pulmonary fibrosis (IPF) and patients with idiopathic PAH (IPAH). The SSc patients were 9 years younger on average than the IPF patients and 5 years older than the IPAH patients. Early deaths occurred more frequently in the SSc group: 7 SSc patients (24%) died during the first month, 4 from primary graft failure and 3 from bacterial infection. The 4 fatal cases of primary graft failure occurred in patients who had undergone single LT for PAH, a therapeutic approach that is now being more rarely used. During the first 6 months, the risk of death in the SSc group was 70% higher than in the IPF group and 52% higher than in the IPAH group. However, these differences did not reach any statistical significance.

More recently, in a study by Saggar et al., 14 SSc patients were compared to 38 patients with IPF all of whom underwent bilateral LT [24]. The SSc patients met quite stringent selection criteria to be transplanted, including the absence of severe gastrointestinal manifestations and other non-controlled visceral manifestations. The SSc patients were still younger than the IPF patients (53 vs 59 years, *P* = 0.02) and their 1- and 2-year survival rates were 93% and 80%, respectively, similar to IPF patients. Three deaths (21%) occurred during a median follow-up of 21 months in the SSc group which is the best result among all studies reported so far and was better than the 62% observed in our cohort after a median follow-up of 7 months. In Saggar et al. study, deaths were attributed to SRC, complications of

### Table II

<table>
<thead>
<tr>
<th>Patients No</th>
<th>Date of transplantation</th>
<th>Time of follow-up</th>
<th>Outcome</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Feb. 1993</td>
<td>74 months</td>
<td>Dead</td>
<td>Faecal peritonitis</td>
</tr>
<tr>
<td>2</td>
<td>May 1994</td>
<td>83 months</td>
<td>Dead</td>
<td>BOS</td>
</tr>
<tr>
<td>3</td>
<td>Dec. 2000</td>
<td>133 months</td>
<td>Alive</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>Oct. 2003</td>
<td>44 months</td>
<td>Dead</td>
<td>Renal insufficiency</td>
</tr>
<tr>
<td>5</td>
<td>May 2008</td>
<td>45 months</td>
<td>Alive</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>Jan. 2009</td>
<td>5 months</td>
<td>Dead</td>
<td>Septicaemia S. aureus</td>
</tr>
<tr>
<td>7</td>
<td>Jul. 2009</td>
<td>7 months</td>
<td>Dead</td>
<td>Multifactorial cause</td>
</tr>
<tr>
<td>8</td>
<td>Oct. 2009</td>
<td>28 months</td>
<td>Alive</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>Sep. 2010</td>
<td>21 days</td>
<td>Dead</td>
<td>Primary graft dysfunction</td>
</tr>
<tr>
<td>10</td>
<td>Dec. 2010</td>
<td>20 days</td>
<td>Dead</td>
<td>S. aureus pneumoniae, septic shock with acute renal insufficiency</td>
</tr>
<tr>
<td>11</td>
<td>Feb. 2012</td>
<td>5 months</td>
<td>Alive</td>
<td>–</td>
</tr>
<tr>
<td>12</td>
<td>Jun. 2012</td>
<td>1 months</td>
<td>Alive</td>
<td>–</td>
</tr>
<tr>
<td>13</td>
<td>Jul. 2012</td>
<td>3 days</td>
<td>Dead</td>
<td>Acute cerebellar infarction</td>
</tr>
</tbody>
</table>

BOS: bronchiolitis obliterans syndrom.
induction anaesthesia in one patient with severe unknown PAH and complications of BOS, respectively. The SSC patients had a higher rate of acute rejection (69% during the first year) but the rate of chronic rejection, marked by the onset of BOS, was similar (48% at 3 years). A similar risk of BOS in the SSC population was reassuring, since BOS is considered as one of the most important prognostic factor after LT. There was no difference in terms of infection. In comparison with the historical series of Massad et al. [26], the 1-year survival rate was better. Differences in terms of experience of the transplantation teams and more stringent selection criteria of SSC patients might contribute to these results. Interestingly, there was no recurrence of ILD or PAH in these patients. To summarize, 2-year overall survival rate was 52–80%.

Taken together, these data suggest that the prognosis of (H) LT can be improved with better selection, pre- and post-transplant management and the choice of double rather than single LT. Indeed, the study with the best survival outcomes had more stringent exclusion criteria [24]. There seems to be a higher frequency of acute rejection and early complications but the rate of chronic rejection and infections appears to be identical.

**Indications for LT/HLT in systemic sclerosis**

The ISHLT, the American Thoracic Society (ATS) and the European Respiratory Society (ERS) published joint guidelines in 1998 on general indications and contraindications for LT/HLT [39]. A revised version of the ISHLT guidelines was published in 2006. The latter guidelines differentiated between the criteria for referring a patient to a transplantation center and the criteria for listing a patient for transplantation [31]. However, in the absence of robust data in the literature, none of these international guidelines specifically addresses the issue of HLT or LT in the context of connective tissue disease [31]. Consequently, the referring process for LT in SSC patients still remains a case-by-case decision.

We aimed herein to summarize the Working Group suggestions in addition to general recommendations from the ISHLT guidelines that can also be applied to patients with SSC. First, SSC *per se* should not be considered as an a priori contraindication for a pre-transplantation assessment [31]. Second, a SSC patient whose lung disease is severe or is worsening despite optimal treatment has to be evaluated in a specialized LT/HLT centre if there is no obvious contraindication (see box 1). Third, (H)LT is indicated for patients with chronic end-stage lung disease who are failing maximal medical therapy, or for whom no effective medical therapy exists. In general, referral for transplantation assessment is advisable when patients have a less than 50%, 2- to 3-year predicted survival or New York Heart Association (NYHA) class III or IV level of function, or both, despite optimal treatment [31].

**Interstitial lung disease**

The 2006 ISHLT recommendations concerned IPF and non-specific interstitial pneumonia (NSIP) [31]. A diagnosis of IPF

**Box 1**

**International absolute and relative contraindications for (heart)/lung transplantation and proposed specific contraindications for lung or (heart)-lung transplantation in systemic sclerosis**

**Absolute contraindications**

- Untreatable organ failure other than lung (especially creatinine clearance < 50 mL/min/1.73 m² using the modification of diet in renal disease formula, liver);
- Non-curable chronic extrapulmonary infection including chronic active viral hepatitis B, hepatitis C, HIV;
- Active or recent neoplasia (less than 2 years), except for basal cell or squamous cutaneous tumours and fully resected carcinomas in situ. A waiting period of 5 years is recommended for high grade tumours of the colon, breast and kidney and for melanomas of stage III or above;
- Active smoking or other substance addiction within the last 6 months;
- Uncontrolled psychiatric or psychological disorders associated with the inability to cooperate or comply with medical therapy;
- Major spinal/thoracic deformity and degenerative neuromuscular diseases likely to seriously impair ventilation mechanics;
- Documented non-adherence with medical therapy or follow-up;
- Body mass index (BMI) < 15 kg/m².

**Relative contraindications**

- Age > 65 years for single or bilateral LT, and > 55 years for HLT;
- Severe or symptomatic osteoporosis;
- Previous thoracic surgery;
- Under nutrition (15 < BMI < 17 kg/m²) or obesity (BMI > 30 kg/m²);
- Invasive mechanical ventilation;
- Colonisation with resistant bacteria, fungi or mycobacteria;
- Severe loss of autonomy with poor rehabilitation potential;
- Uncontrolled comorbidities (systemic hypertension, diabetes mellitus).

**Proposed systemic sclerosis specific contraindications**

- Uncontrolled active inflammatory myopathy; progressive myopathy; myopathy with diaphragm involvement;
- Digital ulcers:
  - > 1 severe episode/year despite optimal treatment;
  - active digital ulcer: temporary contraindication.
- Gastrointestinal:
  - oesophageal stricture;
  - active and severe upper gastrointestinal ulcerations despite optimal treatment, including proton pump inhibitors and prokinetics;
  - high grade dysplasia in a Barrett’s esophagus;
  - gastroparesis (abnormal gastric emptying [< 25% clearance at 90 min post-ingestion]) despite medical treatment;
  - chronic gastrointestinal bleeding with or without anaemia;
  - symptomatic involvement of the small intestine, such as

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or fibrotic NSIP was reported as in itself an indication to refer patients to a transplantation center [31]. Then, the recommendations for the inscription on the transplantation list for ILD patients were as follows:

- **IPF:**
  - diffusing capacity for carbon monoxide (DLCO) < 39% of the predicted level,
  - a 10% or greater decrease in forced vital capacity (FVC) or a 15% decrease in DLCO in a 6-month period,
  - saturation < 88% during 6-minute walk test (6-MWT),
  - honeycombing on HRCT (fibrosis score > 2);
- **NSIP and:**
  - DLCO < 35%,
  - a 10% or greater decrease in FVC or a 15% decrease in DLCO in a 6-month period.

The Working Group felt that the recommendations for IPF had to be adapted to the SSc patients’ specificities [40]. First, NSIP is the most frequent histological pattern in SSc. There is no difference in survival between patients with histological usual interstitial pneumonia (UIP) and NSIP in SSc, which makes a huge difference with IPF [41]. Second, the overall prognosis of SSc-related ILD, even for histological or radiological UIP patterns, is much better than in IPF [41]. Third, the frequency of ILD in SSc precludes any systematic referral of each patient to a transplantation centre as soon as the diagnosis of ILD is made [5].

Goh et al. have recently proposed a simple and robust staging system for SSc-related ILD integrating FVC and extension on the HRCT (whatever the pattern) with a strong prognosis value [42]. Patients with an extensive ILD have a worse survival and functional prognosis than patients with limited ILD [42]. A low DLCO, presence of pulmonary hypertension and male sex were also associated with a worse prognosis in this study as well as in others [42–44]. Presence of an extensive ILD and PH in the same group of SSc patients is associated with a much worse prognosis than ILD or PH alone. Moreover, treatment of PH does not seem to significantly improve the prognosis of these SSc patients with both extensive ILD and PH [6, 43–45]. In addition, some patients with ILD remain strikingly stable over time, suggesting that ILD evolution clinically and/or PFT-based appears to be crucial decision criteria [46]. Finally, although the treatment is not clearly validated, two studies have suggested that cyclophosphamide could be beneficial for treating SSc-related ILD. Both of these studies have shown improvements in FVC based on oral [47] or intravenous [48] cyclophosphamide regimen respectively. A phase 2 study has also suggested that autologous stem cell transplantation supporting high dose of cyclophosphamide could improve SSc-related ILD (2 phase 3 randomized controlled trial are currently addressing this issue) [49] and one retrospective study showed that 6 months intravenous cyclophosphamide followed by oral azathioprine could stabilize a worsening ILD in patients with SSc [50].

Based on these results, the Working Group suggests that the following SSc patients with ILD should be referred to a transplantation centre, in the absence of obvious contraindications (see box 7), to assess the feasibility of LT and identify the optimal timing for inscription on the waiting list:

- worsening (defined by a decline of FVC levels of > 10% or DLCO levels of > 15%) of an extensive ILD (defined by the staging system proposed by Goh et al. [42]) despite an optimal medical approach (based on at least 6 months intravenous cyclophosphamide);
- DLCO < 35% despite an optimal medical approach (based on at least 6 months intravenous cyclophosphamide);
- coexistence of an extensive ILD and PH on right heart catheterization (whatever the value of mPAP).

### Pulmonary arterial hypertension

In 2006, ISHLT proposed the following guidelines to refer a patient with IPAH to a transplantation center:

- NYHA functional class IV irrespective of ongoing therapy;
- rapidly progressive disease.

The guidelines for transplantation were:

- NYHA class III or IV irrespective of ongoing therapy;
- a low (< 350 m) or declining 6-MWT;
• failure of treatment with intravenous prostacyclin, or equivalent;
• cardiac index of less than 2 L/min/m²;
• RAP > 15 mmHg.

According to ESC/ERS guidelines for the treatment of patients with PAH, Galié et al. have highlighted that “in any case, patients with features identifying a worse prognosis profile despite maximal medical therapy should be referred for transplant listing” [51]. The features identifying a worse prognosis were: clinical evidence of right ventricular failure, rapid progression of symptoms, syncope, NYHA functional class IV, 6-MWT less than 300 m, peak O₂ consumption less than 12 mL/min/Kg, very high or rising BNP or NT-pro BNP levels, pericardial effusion, TAPSE < 1.5 cm, RAP > 15 mmHg and cardiac index less than 2 L/min/m².

However, the Working Group stated that some specificities of SSc-related PAH must be highlighted to adapt these recommendations to SSc [52,53]. First, the overall prognosis of SSc-related PAH is still worse than in IPAH with a 3-year survival ranging between 50% and 60% [11,3,54]. Second, in the literature, quite consensual prognosis factors of patients with SSc-related PAH are: age, NYHA functional class III or IV, low DLCO, impaired hemodynamic parameters (mainly low cardiac index and high pulmonary vascular resistance) and presence of ILD [13,55–57]. A recent meta-analysis confirmed that RAP was a significant predictor of survival [11]. Conversely, 6-MWT is a difficult issue in SSc. The meta-analysis also confirmed that baseline 6-MWT was significantly associated with the prognosis in SSc-associated PAH [11]. However 6-MWT reliability and validity may be reduced by many SSc comorbidities including pain, musculoskeletal dysfunction and depression [58]. Therefore, 6-MWT should be carefully analyzed in the context of possible confounders and can be difficult to interpret in a single SSc patient. Lastly, PVOD appears as an overlooked pulmonary vascular disease in patients presenting with SSc-PAH. However, awareness is important considering the worse prognosis and the very poor response to available therapy and the risk of pulmonary edema with the use of vasodilators in this condition [18,35,59,60].

Based on these results, the Working Group proposed the following adapted criteria for referring a SSc patient to a transplantation center:
• NYHA III/IV and/or clinical evidence of right ventricular failure and/or rapid progression of symptoms, despite optimal PAH treatment;
• cardiac index of less than 2 L/min/m² or RAP > 15 mmHg despite optimal PAH treatment;
• in the case of suspected PVOD, patients should be referred to an LT/HLT centre as soon as it is diagnosed irrespective of the patient’s NYHA functional class, mainly because of the high risk edema associated with specific PAH treatment. The use of specific PAH treatment, such as prostacyclin or oral drug with careful monitoring of side effects as a bridge to transplantation will be made on a case-by-case basis [59].

Contraindications for LT/HLT in patients with systemic sclerosis

There are no official specific contraindications for transplantation in SSc patients. One can therefore consider the recognised absolute contraindications for LT/HLT as the starting point and then take into account the particularities relating to SSc [31]. The absolute and relative official contraindications are summarized in box 1. The Working Group also suggested in box 1 SSc specific contraindications based on part on data in the literature, [24,27] and in part on the experience gained by our cases report. The aim of these suggestions is to minimize the risk of short- and long-term SSc specific post-(H)LT complications. Moreover, the gastrointestinal contraindications are highlighted, as it appears to be a major challenge in SSc. As opposed to the study by Saggar et al. [24], oesophageal dysmotility in the absence of severe complications was not considered as an absolute contraindication by the Working Group. In other words, a patient should probably not be excluded only because of an abnormal oesophageal manometry, 24h-pH metry and/or of a multichannel impedance monitoring. According to the recent conclusions by de Perrot et al. [25], we felt that oesophageal dysmotility may instead be considered for an antireflux surgery approach in the post-LT period. This option is discussed below. However, these SSc specific contraindications have not yet been validated by prospective studies and should therefore be considered as suggestions and a guide to decision-making on a case-by-case basis. Some of these contraindications may be temporary as they may be improved by treatment over time.

Pre-transplant assessment

The aim of the pre-transplant assessment is to identify the feasibility and the risk of complications of LT/HLT in SSc patients. This includes seeking any temporary or permanent contraindications (see box 1) in addition to evaluating the extent of the SSc and ensuring optimal management of the pre-, per- and postoperative periods. While some evaluation data are already widely used and were proven effective, the Working Group also discusses investigation methods that need to be evaluated. Pre-transplant assessment is summarized in table III.

Vascular involvement

Digital ulcers

General data

DU have an estimated prevalence between 35% and 58% [61,62]. They often recur, may take more than 6 months to heal and can be complicated by skin infection and/or osteoarthritis [63,64]. Many episodes of DU in the past have raised
| Table III |
| Pre-transplant assessment in patients with systemic sclerosis for the inscription on the waiting list for lung or heart-lung transplantation |

<table>
<thead>
<tr>
<th>Clinical evaluation</th>
<th>Systematic paraclinical evaluation</th>
<th>Other investigations to be evaluated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peripheral vascular involvement</strong></td>
<td><strong>History:</strong></td>
<td>X-ray examination of hands and feet (calcifications and osteitis)</td>
</tr>
<tr>
<td>Date of onset of Raynaud’s phenomenon</td>
<td>Arterial echo-Doppler of upper and lower limbs to look for signs of macrovascular involvement likely to increase the risk of microvascular lesions</td>
<td></td>
</tr>
<tr>
<td>Time before occurrence of first DU</td>
<td></td>
<td>If osteitis/osteoarthritis is suspected; MRI of the hands and/or feet</td>
</tr>
<tr>
<td>Number of previous DU episodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main causal mechanism of the DU (pure ischaemic, mechanical or associated with calcinosis)</td>
<td></td>
<td></td>
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<tr>
<td>History of associated digital ischemia</td>
<td></td>
<td></td>
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<tr>
<td>Previous and current tobacco smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ongoing medication (vasoconstrictors)</td>
<td></td>
<td></td>
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<tr>
<td><strong>Clinical examination</strong></td>
<td></td>
<td></td>
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<tr>
<td>Presence and numbers of active ulcers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of scars on digital pulp and toes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of ulcers during the prior 12 months</td>
<td>Allen test results</td>
<td></td>
</tr>
<tr>
<td>Presence of peripheral pulses and arterial murmur</td>
<td></td>
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</tr>
</tbody>
</table>

| **Kidney involvement** | | |
| Urea, plasma creatinine level and glomerular the modification of diet in renal disease (MDRD) formula | | |
| Urine dipstick test and urinary sediment, 24-h proteinuria, urine cytobacteriological echography | | |
| Anti-RNA polymerase III antibodies status | Elucidate any renal sediment abnormalities prior to LT/HLT | |

| **Digestive tract** | **Esophagus** | | Laboratory tests for malabsorption: |
| Dysphagia/odynophagia | Cough | Hemoglobin | |
| Retrosternal pain | | Iron, folates and B12 vitamin deficiency | |
| Pyrosis, regurgitation | | B1, B6, A, D, and E vitamins | |
| DeMeester severity score77 | | Prealbumin and albumin | |
| Stomach | Early satiety | | |
| Vomiting/nausea | | Abdominal X-ray and CT scan | |
| Anorexia | | Upper endoscopy/manometry/pH metry/multichannel impedance monitoring | |
| **Malabsorption** | | Gastric emptying study by scintigraphy | |
| Weight loss | | Gastrointestinal surgeon consultation | |
| Diarrhoea | | | |
| **Intestinal pseudo-obstruction** | | Glucose breath test | |
| Abdominal pain | | | |
| Constipation | | | |
| Bloating | | | |

| **Muscle involvement** | **Myalgia** | | CPK, LDH and aldolase serum levels |
| Exercise intolerance | Amyotrophy, muscle deficit by muscle testing | Electromyogram | |
| | | Chest X-ray with inspiration and expiration images and sniff test during the pulmonary function tests for diaphragmatic involvement | |

| **Heart involvement** | Palpitations, lipothymia and syncope | | EKG and 24-h-Holter EKG (followed by electrophysiological investigations if appropriate) |
| Chest pain | Doppler echocardiography | | |
| Heart rate | Isotopic evaluation of systolic function if poor echogenicity | | |
| Arterial pressure | Right heart catheterization with filling test coupled with left cardiac catheterisation and coronaryography | | |
| Valvular murmur | | | |
| Oedema | | | |
| Jugular turgescence | | | |
| Pericarditis | | | |

DU: digital ulcers; MRI: magnetic resonance imaging; (H)LT: (Heart)-lung transplantation.
fears regarding critical digital ischemia in the post-transplantation period.

Evaluation
Pre-transplantation evaluation for DU is summarized in table III and aims to stratify the risk of post-transplantation recurrence.

Kidney involvement

Rationale
SRC is the predominant type of kidney involvement in SSc [65–68]. It is the only specific life-threatening form of acute renal failure likely to be induced by the transplantation procedure. The incidence of this complication is declining, and the prevalence of SRC is currently 4–6% of patients, with a marked predominance of patients with early (first 3 to 4 years) and diffuse cutaneous forms [65,69]. SRC is defined by the abrupt onset and/or rapid progression of severe arterial hypertension (>150/85 mmHg, obtained on at least two occasions within 24 h), and/or rapidly progressive, otherwise unexplained renal insufficiency, which may be oliguric. However, in 10% of cases, arterial blood pressure is normal, indicating normotensive SRC. Forty-three per cent of cases present thrombotic microangiopathy, defined as an association of mechanical haemolytic anaemia with the presence of schizocytes on blood smears, usually moderate thrombopenia, reduced haptoglobin level and increased LDH and free bilirubin levels. A renal biopsy is not essential for the diagnosis but may be very useful in atypical forms (e.g. normotensive forms), in the presence of haematuria, or to ascertain the diagnosis if necessary during the post-transplantation period. Some risk factors that are predictive of SRC (some of them can be directly related to the HLT/LT, such as high dose corticosteroids treatment or anaemia), are as follows [65,66,68,69]:
- diffuse cutaneous involvement;
- rapid progression of skin thickening;
- SSc duration < 3 years;
- recent cardiac event;
- pericarditis;
- left ventricular insufficiency;
- recent onset of anaemia;
- presence of anti-RNA polymerase III antibodies;
- treatment with prednisone or equivalent > 15 mg/day within the previous 3 months.

Vasomotor phenomena have also been implicated, with the description of a decrease in renal cortical blood flow when SSc patients are exposed to cold or to vasoactive amines, commonly used post-transplantation. In addition to corticosteroids treatment, a number of drugs have also been implicated, especially cyclosporin A (CSA), which is also commonly used post-LT/HLT [70]. This led the Working Group discuss alternative immunosuppressants in the anti-rejection treatment section.

Evaluation
Pre-transplantation evaluation of renal involvement is summarized in table III.

Digestive tract

Gastro-oesophageal reflux

Rationale
Oesophageal involvement – the low oesophageal sphincter and the lower third of the esophagus – affects 50–90% of SSc patients. Oesophageal manometric disturbances are associated with a significantly decreased DLCO and higher frequency of ILD in the following 18 months [71]. Second, the presence of acid or non-acid GERD and especially the number of GERD episodes and proximal GERD are associated with more severe ILD [72]. Moreover, GERD is a major problem in the context of LT/HLT for two reasons:

1. LT may exacerbate the GERD (as well as gastroparesis) because the surgical procedure may injure the vagus nerve. Immunosuppressive therapy also has a negative impact on gastric emptying;

2. GERD might increase the risk of chronic rejection.

Indeed, GERD, especially non-acid GERD is associated with the occurrence of BOS [73], which is the leading cause of high morbidity and mortality after LT, although a direct link between BOS and GERD is still a matter of debate. This risk of BOS is proportional to the concentration of bile salts in the bronchoalveolar lavage fluid [74–76]. Therefore, management of GERD before and after LT appears as a major challenge in patients with SSc [77].

Evaluation
Pre-transplantation evaluation of oesophageal and other digestive involvement is summarized in table III. Symptoms of GERD being non-specific [78,79] upper endoscopy, oesophageal manometry and 24h-pH metry, are required to determine GERD severity and proximal or distal oesophageal involvement [80]. The DeMeester Severity Score, a composite score made up of all the factors quantified in the ph metry, should also be calculated [81]. Despite few evaluations, the Working Group recommends multichannel impedance monitoring to evaluate acid and non-acid refluxes and identify which oesophageal part is involved [82].

Gastrointestinal surgeon consultation

The Working Group proposes that, prior to LT/HLT, all transplant candidates presenting GERD and/or significantly abnormal oesophageal motility should systematically be evaluated by an experienced surgeon to discuss indications and timing for antireflux surgery in the post-transplant period. Indeed, results of several studies have suggested that antireflux surgery in the post-transplant period may reduce the risk of developing BOS [79,83]. Prospective studies assessing this strategy are eagerly awaited.
Gastroparis

Gastroparis is present in up to 50% of SSC patients [84]. It most commonly manifests as early satiety, vomiting nausea and anorexia. Gastric emptying study based on a scintigraphy including up to 4 h images confirms the diagnosis if more than 10% of the meal is present in the stomach after this delay [84]. Gastric emptying scintigraphy is considered by the Working Group as the gold standard method for gastroparesis diagnosis (table III). This test performed postoperatively may also help identifying gastroparesis resulting from vagus nerve injury.

Malabsorption syndrome and intestinal pseudo-obstruction

Malabsorption syndrome also occurs frequently and manifests as abdominal pain, bloating, diarrhea and weight loss. It can be promoted by bacterial overgrowth, which can be diagnosed using the glucose breath test. Patients presenting recurrent constipation may develop a pseudo-obstruction or even an actual obstruction. In such cases, an abdominal CT scan should be performed.

Skeletal muscle involvement

Rationale

The frequency of myopathies associated with systemic sclerosis is highly variable, ranging in the literature from 14% to 81% according to the series [85,86]. In most cases, the clinical picture is incomplete, associating myalgia, a discrete proximal weakness and a moderate increase of muscle enzymes (2 to 3 times the normal level). In 5% of cases, muscle involvement appears as an associated inflammatory myopathy [85,86]. In this setting, the deficit may be more pronounced and pathologic findings usually show variable signs of inflammatory myopathy. In addition to this general view, it is important to note that the diaphragm may also be involved in an inflammatory and dysfunctional process and therefore be considered as an absolute contraindication for LT/HLT. Due to phrenic nerve surgical injury, diaphragm dysfunction may also appear and/or exacerbate during the short-term postoperative period.

Evaluation

Pre-transplantation evaluation of skeletal muscle involvement is summarized in table III.

Cardiac involvement

Rationale

SSc affects the myocardium with a myocardial fibrosis resulting from multiple focal ischaemic lesions [87]. All the other cardiac structures may also be affected [88–90]. Cardiac involvement is as frequent in limited forms as in diffuse forms but is particularly prevalent in patients with anti-Scl70 and a rapid increase in Rodnan score. Myocardial involvement is a virtually constant histological finding but rarely causes left ventricular systolic dysfunction (approximately 5–10% of patients with cardiac involvement, principally male and with associated inflammatory myopathy) [91]. In contrast, diastolic dysfunction of the right ventricle and left ventricle is far more frequent, occurring in 30% to 50% in some series [92–96]. A strict cardiac evaluation prior to transplantation is required, as this diastolic dysfunction may complicate the postoperative course. Rhythm and conduction disturbances are frequent in the course of SSC and increased during the follow-up of the disease [95,97]. Supraventricular tachycardia is the most common manifestation and ventricular arrhythmia (extrasystoles or episodes of ventricular tachycardia) the rarest. They are due to the myocardial fibrosis, cardiac dysautonomia and involvement of the conduction system [98,99]. Pericardial involvement is observed in about 15% of patients.

Evaluation

Pre-transplantation evaluation of heart involvement is summarized in table III. The diastolic function should be assessed using a filling test during right heart catheterisation, coupled with left heart catheterisation, with measurement of telediastolic pressure of the left ventricle and coronaryography, as recently recommended [100]. The place of MRI and echocardiography with the tissue Doppler modality needs to be clarified [94,101]. These two techniques are characterized by a sensitive detection threshold for the diagnosis of cardiac involvement in SSC and may provide complementary data to standard echocardiography. In addition, cardiac MRI enables a precise analysis of the different patterns of heart involvement in SSC by differentiating morphological, functional, perfusion, and delayed contrast enhancement abnormalities. Compared with other imaging modalities, cardiac MRI detects significantly compromised RV function in a higher number of patients with asymptomatic SSC and thus may become an invaluable tool in detecting subclinical involvement in these patients [101,102]. Therefore, the Working Group suggests that cardiac MRI should systematically be performed to explore the presence and characterize the severity of myocardial involvement prior to LT/HLT. However, prospective studies are still needed to clarify this attitude.

Monitoring of patients on the waiting list

Clinical status of SSC patients on the waiting list for LT and HLT may rapidly deteriorate. The Working Group suggests that their referring SSC physician should clinically evaluate SSC patients at least once in a month. These visits may also provide time points for optimizing treatment and detecting temporary or definitive contraindications for LT/HLT (reduction of BMI, occurrence of DU, etc.) When placed on the waiting list for single or double LT, patients should be clinically evaluated on a 3-month basis to detect heart dysfunction and assess whether HLT could become a more appropriate option. For example, in patients with ILD and waiting for a single or double LT, regular echocardiography should assess the occurrence of a high systolic pulmonary
arterial pressure. Each referring physician should bear in mind that any suspicion of PH development (or worsening) should be followed by a new invasive haemodynamic evaluation.

Pre-transplant management

Based on a multidisciplinary approach, prevention and treatment of the various SSC manifestations must be optimised to promote the best condition of LT/HLT candidates and delay development of irreversible contraindication to the surgical procedure. Moreover, official guidelines regarding the global management of SSC have been formally established by european experts from the framework of the EULAR recommendations [103].

With regard to DUs, patient awareness remains essential. Patients must be instructed on how to protect themselves from the cold and from inclement weather. In terms of treatment, calcic inhibitors should be used extensively in patients with Raynaud’s phenomenon. In the case of recurrent ulcers, bosentan has now received marketing approval for DU prevention in the context of SSC [104]. However, one must highlight that interactions between plasma levels bosentan, CSA and tacrolimus may appear when these therapies are associated [105]. Indeed, bosentan can decrease the area under the curve of CSA and tacrolimus and doses adjustments may sometimes be necessary. Conversely, CSA and tacrolimus can increase bosentan plasma concentrations and liver toxicity. Therefore, while bosentan is usually considered contra-indicated if CSA is prescribed, a careful monitoring is mandatory when tacrolimus and bosentan are associated to prevent bosentan main side effects (hepatotoxicity, anemia) [105]. Of note, there are no major interactions between tacrolimus and ambrisentan [105] although close monitoring of tacrolimus residual dose is also required and limitation of ambrisentan dose to 5 mg/d is required [105].

The risk of SRC is higher during the postoperative period. Therefore, it appears a major importance to control prior to LT/HLT each SRC risk factors including systemic arterial hypertension. In that context, if systemic hypertension is confirmed, the Working Group proposes that first-line therapy should be based on ACE inhibitors [8]. In the absence of arterial hypertension, the systematic use of ACE inhibitors for SRC prevention is still a matter of debate. However, the Working Group considers that use of ACE inhibitors is not supported by an accurate level of proof in that context, and may additionally be deleterious [106] and therefore should not be recommended with the current knowledge. The use of nephrotoxic treatments should be avoided as much as possible and a highest haemoglobin concentration should be targeted to ensure satisfactory renal perfusion. When corticosteroids are indicated, the Working Group suggests that their dose should be maintained at the lowest effective level and in any cases ≤ 15 mg/day.

Choice of surgical procedure

Although some advances have been achieved regarding surgical techniques in lung transplantation over time, it remains unclear which option (i.e. single lung, double lung or heart-lung transplantation) provides the best benefits in terms of survival, time on the waiting list, and transplantable lungs allocation. By their properties in inducing DU and digital necrosis, renal failure or gastrointestinal ischemia, the use of vasoconstrictive agents during the postoperative period may be challenging in SSC and should therefore be restricted to minimal. In addition, the choice of the surgical technique should also take into account the need for such therapies support during the postoperative time. It is now well admitted that single LT improves donor organ allocation, decreases time on the waiting list and therefore mortality among transplantation candidates. However, in patients with PH, single LT is associated with a poor outcome and should therefore be strongly discouraged in SSC patients with any significant elevation of pulmonary arterial pressure. However, this surgical procedure could be an option particularly in patients with a previous history of thoracotomy once PH has formally been ruled out. The single LT procedure should preferably concern the lung from the largest chest cavity for providing a maximal parenchymal reserve. However, even in the absence of PH, it is now well established in IPF patients that compared to single LT, double LT provides a better long-term outcome in term of survival and risk of BOS [107].

In the subset of patients with PH, the choice between double LT and HLT depends mainly on heart status, and more specifically on ability of the right ventricle to rapidly recover after double LT. Regarding SSC patients, this issue remains even more problematic due to the SSC intrinsic risk of heart involvement [91,93,95,101,108,109]. Indeed, the rationale for choosing double LT in PH patients relates to the fact that right heart function is likely to improve once pulmonary pressures drop after surgery. However, severe long-standing PH may also be associated with right ventricular muscle hypertrophy, which may favour a postoperative hyperdynamic state and thus pulmonary edema. High dose inotropic drug therapy early in the postoperative course worsens the outflow obstruction. Early postoperative course after double LT for end-stage PH may be complicated by a transient left ventricular dysfunction characterized by high left atrial pressure, high pulmonary arterial pressure, and graft dysfunction. Echocardiography usually shows enlargement and thickening of the right ventricle with paradoxical septal motion [110]. This finding is consistent with a transient compliance disorder of a small left ventricular cavity.

In our experience like in other, the choice of HLT vs double LT is based on preoperative inotropic requirements and on the presence of major right ventricular enlargement or severe right heart dysfunction. Thus, HLT is considered the surgical
procedure of choice in patients with severe chronic right ventricle dysfunction requiring inotropic support and/or complicated by renal failure, bilirubin increase, right atrial pressure over 20 mmHg or major right heart enlargement on cardiac imaging. HLT may also be proposed in patients with severe coronary artery disease, in whom a percutaneous revascularization may not be easily performed.

Additional clinical issues in SSc patients require further concerns. First, while a major and persistent pericardial effusion in non-SSc patients is usually correlated with severe PH and may indicate the need for HLT, pericardial effusion may be observed in the context of SSc without severe PH and controlled by a low dose of prednisone. The absence of response to prednisone could be one further argument for HLT. Further, major concerns regard the worse post-LT prognosis of SSc patients who specifically present with major left ventricular diastolic dysfunction, ILD and no or mild PH [96]. In that context, the diagnosis of severe diastolic LV dysfunction could be suggested by heart failure symptoms associated with high BNP or NT-pro BNP values, resisting to diuretics and should be based on echocardiography findings and/or ideally during the right/left heart catheterization associated with a filling challenge. In patients with PH, the presence of a significant diastolic LV dysfunction may be harder to identify. However, given its impact on outcome and its poor response to conventional medical therapies, the Working Group suggests that left heart diastolic dysfunction may preferably require HLT rather than LT. Last, a growing body of evidence have emphasized the significant role of right ventricle dysfunction on prognosis in PH patients. Several non-invasive markers mainly based on Doppler echocardiography or cardiac MRI have emerged as pertinent tools in evaluating right ventricle function [111–113]. Whether these markers may help guiding the choice of surgical procedure (HLT vs double LT) needs to be further investigated.

### During and after transplantation management

#### Management of cutaneous disorders

Prevention of cutaneous complications, mainly DU and digital necrosis, is crucial and the following measures should be considered:

- use heated blankets in the recovery room;
- systematically warm perfusion solutions to room temperature;
- avoid radial artery catheterisation;
- use of vasopressive amines is associated with an increased risk of digital necrosis and should be limited if possible. If calcium channel blockers have been interrupted, they should be reintroduced as soon as possible. In the case of prolonged digital ischaemia, treatment with iloprost can be proposed in accordance with the patient’s haemodynamic status and before necrotic lesions occur [114,115]. If ischaemic necrosis develops, anticoagulant therapy could be proposed in the absence of specific contraindications especially related to the surgical procedure or the gastrointestinal risks of bleeding.

#### Prevention and treatment of SRC

A satisfactory hydration level in each SSc patient should be maintained and may help preventing acute renal failure. The use of potentially nephrotoxic treatments, including injections of contrast media, should be avoided as much as possible. A high haemoglobin concentration should be targeted to ensure satisfactory renal perfusion and, if arterial hypertension is present, introducing ACE inhibitors may be beneficial. Compared to ACE inhibitors, angiotensin II receptor antagonists do not seem to be as effective for the treatment of SRC. Corticosteroids dose and choice of the anti-rejection treatment, which can favour the occurrence of SRC, are discussed below. The Working Group considers that screening for SRC during the follow-up is of major importance and should include regular blood pressure measurements and detection of thrombotic microangiopathy based on haptoglobin and schizocytes dosages.

SRC should be suspected in patients presenting with acute onset and/or progressive worsening of arterial hypertension (> 150/85 mmHg, confirmed during at least 2 different measurements) and/or rapidly progressive renal insufficiency, possibly oligo-anuric in the absence of alternative diagnosis. Biological assessment will include creatinine, proteinuria and haematuria, and detection for thrombotic microangiopathy. A renal echography should be performed to rule out any obstruction. If diagnosis remains unclear, a renal biopsy may be useful.

Treatment of SRC is consensually based on controlling systemic arterial pressure by using an ACE inhibitor [69] with a short half-life, such as captopril. Treatment dose is progressively increased to target 150 mg/day within 48 h. A parenteral calcium channel blocker (nicardipine) should also be administered after the first 48 h if arterial pressure is not significantly reduced by the ACE inhibitor monotherapy. Despite this medical approach, arterial pressure control and/or renal function may still deteriorate and require early dialysis. In normotensive patients, ACE inhibitors should be used cautiously at lower doses to avoid a sustained arterial hypotension which may promote a significant renal hypoperfusion and eventually renal insufficiency.

#### Management of gastro-oesophageal reflux

During the surgical procedure, Trendelenburg position may favour pulmonary aspiration and should therefore be avoided. Once the patient has left the operating room, the top of the bed should be raised to reach a minimum angle of 30°. High dose proton pump inhibitors and a prokinetic agent (like domperidone) should be introduced. Finally, if any difficulties in weaning
the patient off the ventilator, appear a tracheotomy may help protecting the respiratory tract from GERD. Because of concern that GERD increases the risk of BOS, the general trend has been to propose a surgical solution, namely gastric fundoplication, to most of all recipients presenting with significant GERD. Supportive evidence for this strategy is derived from retrospective studies in which gastric fundoplication within 3 months after transplant was associated with greater freedom from BOS and increased survival [102]. Another study from the same center showed that fundoplication improved lung function in many patients with established BOS [103]. Because of the severity of the respiratory disease, the surgical procedure is rarely performed before transplantation [78,79]. However, some authors have reported a clinical stabilisation among listed patients and even, in one case a significant improvement leading to a delisting [116]. Usually, antireflux surgery issue is raised after LT/HLT. In the study by Cantu et al., 60% of patients underwent antireflux surgery within 10 days after transplantation and 100% within 90 days. Total fundoplication (360°) is usually recommended. However, if a complete aperistaltism has been diagnosed by manometry, it will preferably require partial fundoplication (240° either posterior as in Toupet procedure or anterior as in Dor modified procedure), which seems non-inferior in terms of GERD control and well-tolerated according to published studies [78,79].

Before adopting this radical approach for every lung transplant recipient, however, it is important to be aware that:

1. GERD – as well as the cough reflex – may improve over time;
2. Fundoplication may have serious side effects (e.g., significant weight loss, which can be of importance in recipients with significant malnutrition);
3. The protective function of the surgical sleeve may wane over time;
4. The precise indications, timing, and choice of fundoplication technique are yet to be defined;
5. The overall impact on lung function and survival are unknown because there are no controlled studies to date.

Based on a multidisciplinary approach, the Working Group suggests that indication, feasibility and optimal timing for antireflux surgery should be discussed during the post-transplantation period on a case-by-case basis with a particular focus on patients with a severe and/or worsening GERD and/or a severe oesophageal dysmotility. A severe and drug-resistant reflux after LT in the absence of antireflux surgical possibility may require a jejunostomy to ensure proper nutrition, or an early tracheotomy to improve patient weaning off the ventilator.

Management of other gastrointestinal complications

In the event of severe gastroparesis, enteral feeding is advisable. The following drugs can be used: metoclopramide, domperidone and erythromycin [117]. Jejunostomy may be required to ensure proper nutrition. Bacterial overgrowth can be treated with monthly courses of antibiotics and intestinal pseudo-obstruction can be treated with octreotide.

Anti-rejection treatment

Although there is some variability in the medications used at different lung transplant centers, the approach to immunosuppression is generally similar. Maintenance regimens typically involve administration of three distinct classes of immunosuppressive agents: calcineurin inhibitors (CNIs; e.g., CSA, tacrolimus), antiproliferative agents (e.g., azathioprine, MMF, sirolimus), and corticosteroids. In addition, approximately 50% of lung recipients receive induction therapy to increase immunosuppression in the early post-transplant period [118]. CNIs are associated with several and generally dose-dependent side effects, among which acute and chronic renal toxicities remain frequent and of particular concern in the context of SSc [119]. Comparative studies of the CNIs suggest that a tacrolimus-based immunosuppression regimen may have greater efficacy than a CSA-based regimen [120–122]. In a single-center, randomized trial of 133 lung recipients treated with a CNI, azathioprine, and prednisone, patients who received tacrolimus were statistically less likely to develop BOS compared with those who received CSA within 2 years (21.7% vs 38%; P < 0.05) [121]. A smaller study comparing the two CNIs in conjunction with MMF and prednisone showed fewer acute rejection episodes per 100 patient-days in the tacrolimus group versus CSA (0.225 vs 0.426; P < 0.05), although 1-year survival rates were not different [123]. Longer-term follow-up (up to 9 years) of these patients did not reveal differences in acute rejection rates, BOS or survival rates. More recently, in a single-center investigation of 90 patients treated with azathioprine and prednisone and randomized to receive either tacrolimus or CSA, the tacrolimus group demonstrated a lower cumulative burden of acute rejection and lymphocytic bronchiolitis over a median follow-up period of approximately 2 years [124]. Although the data indicate that a tacrolimus-based maintenance immunosuppression regimen is somewhat more effective at reducing rejection rates without an attendant increased risk of infections or malignancies, it is not clear if this beneficial effect is maintained with different combinations of antiproliferative agents (e.g., MMF vs azathioprine). While nephrotoxicity appears to be similar with both drugs, tacrolimus is usually associated with a lower incidence of arterial hypertension [125]. In addition, a randomised crossover study including a small number of heart transplant patients demonstrated that compared to CSA, there were fewer renovascular haemodynamic effects with tacrolimus [126]. In that context, and also because SRC is of major concern in SSc, the Working Group suggests that tacrolimus should be the CNIs of choice in SSc undergoing (H)LT. This proposal is in accordance with the recent
conclusions of the UCLA group [24]. The residual dose aimed for is between 10 and 15 ng/mL with an initial dose of 0.15 mg/kg/day (based on 2 equal doses administered twice in a day) during the first 6 months post-transplant. Maintenance immunosuppression regimens typically include at least one antiproliferative agent, usually azathioprine or MMF. Azathioprine is the oldest drug in this category and is still used by one-third of all transplant centers. Newer agents, such as MMF and sirolimus have been incorporated into immunosuppression protocols at many programs [127]. Although data from other types of solid organ transplantation have demonstrated superior outcomes (including survival) with MMF compared with azathioprine, two prospective, randomized studies have shown no difference in either short-term (6-month rates of acute rejection and survival) or long-term (rates of acute rejection, BOS, and survival) outcomes [128,129]. Combining CSA with MMF leads to a marked reduction in the active metabolite of MMF (mycophenolic acid), which does not occur with tacrolimus. MMF has also been studied as a treatment for SSc, with encouraging results, especially in treating diffuse forms [130]. There is also evidence to suggest that MMF may have antifibrotic properties [131–134]. Based on these results, MMF may be a preferable anti-rejection therapy in this context of SSc. The usual dose is 2 to 3 g (administered in two equal doses).

Corticosteroids are used both during the induction and maintenance phases of anti-rejection therapy after LT. During LT/HLT, in contrast to kidney or heart transplantations, corticosteroids therapy should be regularly administered to limit the effect of the increasing graft immunogenicity over time. The dose of corticosteroids has not yet been well standardised. However, since corticosteroids may increase SRC risk in a dose-dependent way, they should be given at the minimum effective dose in SSc patients undergoing LT or HLT. Induction therapy involves the administration of a potent immunosuppressive agent in the perioperative or early postoperative period to reduce risk of acute rejection and permit more gradual initiation of maintenance immunosuppression including corticosteroids and CNIs. Several types of induction agents are currently in use and specifically target T-lymphocytes, the primary effector cells of the cell-mediated immune system. The most common induction agents used in clinical practice are humanized or chimeric monoclonal antibodies to CD25 (e.g., daclizumab, basiliximab), the alpha subunit of the interleukin-2 receptor (IL-2R). A recent study by Becker et al. suggests that basiliximab could also be useful for treating SSc itself [135].

The Working Group therefore suggests that the immunosuppression regimen in SSc patients undergoing LT/HLT could be based on:
- bolus of 500 mg of methylprednisolone during the operation followed by 0.5 mg/kg/day of prednisone for 3 days and then progressively tapered;
- Tacrolimus 0.15 mg/kg/day in two divided doses to achieve a serum level of between 10 and 15 ng/mL;
- mycophenolate mofetil 1 g twice daily;
- if tacrolimus has to be delayed (e.g. because of renal function), basiliximab 20 mg at day 0 and day 4 is indicated followed by tacrolimus on day 4.

Conclusion
This Working Group position paper is based on the available literature review and on the experience gained in carrying out transplantation in SSc patients. The aim of this position paper is to improve success of the surgical procedure and survival of (heart-)lung transplanted SSc patients. This requires an exhaustive and multidisciplinary presurgical assessment and a postoperative management suitably optimised for SSc patients. The final decision has to be made on an individual basis.

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