

# Recent advances in the diagnosis and treatment of interstitial lung disease in systemic sclerosis (scleroderma): a review

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## ABSTRACT

*Interstitial lung disease (ILD) in systemic sclerosis (scleroderma) is a rare and potentially lethal and devastating autoimmune disease, and yet the cause of it remains poorly understood. It is associated with tissue fibrosis not only in the lungs, but also other organs like the heart and kidneys. Although ILD can manifest itself in various disease presentations, ILD in systemic sclerosis is particularly and especially worrying because it has the highest case-specific mortality among all autoimmune rheumatic conditions. The unsatisfactory clinical outcome and prognosis for ILD in systemic sclerosis has, unsurprisingly, fuelled an intense search for early and accurate diagnosis, as well as new therapeutic strategies. Recent advances in diagnostic techniques and treatment interventions represent a significant step forward in our understanding and management of ILD in systemic sclerosis. Here, we review the current knowledge pertaining to the treatment of ILD in systemic sclerosis, and also address the various challenges involved as well as implications for the future.*

## 1. Introduction

Interstitial lung disease (ILD) in systemic sclerosis (scleroderma) represents a plethora of clinical disorders that can result in widespread tissue transformation and structural damage to lung parenchyma and impairment of respiratory function (1). In pulmonary physiology, ILD is classified as a restrictive lung disease, with a decrease in lung compliance and vital capacity (2). In histological terms, it is characterised by activated fibroblasts, coupled with the production of excess extracellular matrix proteins and biological mediators that are responsible for causing inflammation and fibrosis (3). 4 in

10 patients with systemic sclerosis are estimated to have ILD (with a forced vital capacity (FVC) of less than 75% predicted), and it represents one of the major causes of death for people with systemic sclerosis (4).

While the first published case of ILD in systemic sclerosis was reported 1868, where the American physician Austin Flint wrote in his book *A treatise on the principles and practice of medicine* (1), the documentation of systemic sclerosis itself dates back much further.

The word “scleroderma” is derived from Greek, meaning “hard skin”, and Carlo Curzio, an Italian doctor, first described a patient with scleroderma-like symptoms in 1754. This “hard skin” condition, together with the vasomotor disorder known as Raynaud’s phenomenon (discolouration of the fingers and toes) are the cardinal signs of systemic sclerosis (5).

Therefore, in this review, we seek to explore the various new advances in the diagnosis and treatment of ILD in systemic sclerosis (Table I), and to also address the various clinical guidelines (6) and future implications in hopes of better understanding this complex and potentially lethal disease.

## 2. Epidemiology / demography

Systemic sclerosis is a multi-system autoimmune disease involving the skin and various internal organs including the lungs and the heart (7). Although the exact cause of systemic sclerosis is not known, there is evidence to suggest that genetic inheritance might be implicated (8). Systemic sclerosis can be classified according to the degree of skin thickening and organ involvement into 2 categories: diffuse cutaneous (which harbours a higher risk of heart and kidney damage) and limited cutaneous (9). Fortunately, systemic sclerosis has a

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**Table I.** Overview of the recent advances in the diagnosis and treatment of interstitial lung disease (ILD) in systemic sclerosis.

Class	Treatment	Comments	Ref
Diagnostic	Exhaled nitric oxide	• Able to reflect extent of endothelial damage and lung inflammation	(28-30)
Diagnostic	Denosing thin section computed tomography (CT) images	• More accurate classification of parenchymal abnormality	(37)
Diagnostic	Computer-aided diagnosis (CAD)	• Able to quantify the disease extent	(38)
Diagnostic	Staging algorithm	• Provides discriminatory prognostic information for the disease	(39)
Drug	Rituximab	• Patients successfully treated when they did not respond to prednisolone and cyclophosphamide, but no randomised controlled trials (RCTs) conducted	(42-46)
Drug	Mycophenolate mofetil	• Well-tolerated in patients, but no large RCTs conducted	(47-54)
Drug	Imatinib	• Well-tolerated in patients, but no large RCTs conducted	(56-60)
Drug	Methylprednisolone	• Used in combination with pulsatile cyclophosphamide, but no RCTs conducted	(61,62)
Drug	Cyclophosphamide	• Most wide-used and studied in patients with ILD in systemic sclerosis. • The SLS and FAST study are the only 2 high quality RCTs conducted so far. • EULAR and EUSTAR recommend use.	(67,78,79)
Surgical	Lung transplantation	• Used in end-stage lung fibrosis, but shortage of donors	(80,81)
Cell-based therapy	Stem cell and alveolar type II cells transplantation	• Mesenchymal stem cells can hasten lung repair. • Patient's own alveolar type II cells would circumvent problems of host-graft rejection. • Not routinely performed. • No RCTs conducted.	(82,83,85)

relatively low prevalence, affecting 240 per million in the US and 31 per million in the UK (10).

In addition to microvascular and tissue fibrosis, immunologic disruption is also observed in systemic sclerosis (7). Although renal complications were the leading cause of death prior to the advent of angiotensin-converting enzyme (ACE) inhibitors, pulmonary complications have now assumed that role (11, 12).

Although it might seem that ILD in systemic sclerosis would usually arise as a result from one of the many complications of systemic sclerosis, there is also evidence that ILD in systemic sclerosis could present itself as the initial and only manifestation of systemic sclerosis (13).

### 3. Pathogenesis of ILD in systemic sclerosis

The pathogenesis of ILD in systemic sclerosis is complicated, and involves deviation in homeostasis of both the circulatory and immune system. These biological aberrations often result in microvascular damage due to fibrosis, as well as an upregulation of inflammatory response due to immunologic disturbances (4). It is believed that this would eventually lead to collagen deposition in and fibrosis of the lungs, impairing its function in gas exchange (14, 15) (Fig. 1). Experiments have demonstrated that proteasome inhibitors were able to mitigate lung tissue fibrosis by simultaneously inhibiting collagen production and upregulating collagen degradation (16).

Although the exact pathophysiological and chronological events of ILD in systemic sclerosis are not fully understood (17), there is evidence that gastroesophageal reflux might play a role in its development (18, 19), but this hypothesis remains controversial (20). Thus, the unfavourable clinical outcome correlated with pulmonary complications of systemic sclerosis has fuelled an intense search for new therapeutic strategies with particular emphasis on early and accurate diagnosis (21).

### 4. Advances in diagnostic techniques

ILDs encompass a large cluster of more than 200 different forms, and its clinical manifestations have similar presentations (for instance, breathlessness and widespread shadowing of chest x-rays) (22). Therefore, correctly identifying the different entities of ILDs at the early stages would undoubtedly have significant influence on prognosis.

Although lung biopsies and bronchoalveolar lavage (BAL) have provided insight into the pathogenesis and cellular mechanisms of ILD in systemic sclerosis (23), they are invasive procedures and are therefore not routinely performed. In addition, BAL was not shown to be predictive of response to cyclophosphamide in the Scleroderma Lung Study (SLS) (24). Furthermore, it has also been suggested that BAL is not predictive of future course of ILD in systemic sclerosis (25). Thus, a technique called induced sputum (collecting pulmonary fluids after expectoration) has been propounded as an alternative (26). Also, molecules like von Willebrand factor and soluble E-selectin were also proposed as serum markers for ILD in systemic sclerosis (27).

#### 4.1. Exhaled nitric oxide

Histological and morphological abnormalities observed in high-resolution computed tomography (HRCT) scans do not correlate well with therapy, and is a poor predictor for alveolar inflammation. A new study proposed the measurement of exhaled nitric oxide (NO) (28) as a marker that can reflect the extent of endothelial pathology. Furthermore, it also serves to ascer-

tain the presence of lung inflammation well before the occurrence of fibrosis, including the extent of ILD in systemic sclerosis (29). Although the exact mechanism is not known, it has been suggested that there is an upregulation of nitric oxide synthase and NO production due to mediators of inflammation and cytokines production (30).

#### 4.2. Imaging techniques

General medical consensus dictates that performance of a HRCT scan; a pulmonary function test; a six minute walk test; and dyspnoea measurement via a Borg index are imperative for the initial diagnosis of ILD in systemic sclerosis (31, 32).

A HRCT scan allows clinicians to characterise the nature and extent of lung fibrosis (33). HRCTs would also provide a visual indication of pulmonary fibrosis and ground-glass opacity in lungs (34). Furthermore, evidence shows that pericardial abnormalities (which can occur in patients with ILD) can also be detected by HRCTs (35). Scoring on HRCT scans involves usually involves visual inspection by radiologists coupled with specialised computer programmes to standardise the scoring system (36). The scores that describe lung abnormalities can range from 0 to 4 (0 = absent; 1 = 1–25%; 2 = 26–50%; 3 = 51–75%; 4 = 76–100%).

In order to mitigate variations in assessment procedures and noise variability in computed tomography (CT) scans, a novel technique was recently conducted by denoising CT scans. This protocol contributed to a more precise and streamlined categorisation of lung tissue abnormality in ILD (37) (Fig. 2). Also, a prototype computer-aided diagnosis (CAD) software was recently developed to quantify the disease extent in patients with the disease (38) (Fig. 3). This is of particular significance as the application of CAD provided clinicians the ability to detect fibrotic areas of the lungs that are not usually picked up in regular CT scans.

#### 4.3. Staging algorithm

A novel method has recently been developed, encompassing a composite of HRCT scans, pulmonary function



**Fig. 1.** Respiratory difficulties. X-ray of a fibrotic lung in systemic sclerosis (right). A normal lung (left). Copyright ©Radiological Society of North America. Reproduced with permission from Mayberry JP, Primack SL, Müller NL. Thoracic manifestations of systemic autoimmune disease: radiographic and high-resolution CT findings. *Radiographics* 2000; 20(6): 1623-35.

test data and a construction of a simple staging algorithm. This was subsequently shown to be applicable in routine clinical practice and providing a definitive diagnostic assessment for the disease (39) (Fig. 4).

#### 5. Advances in drug therapy

Under pathological conditions, lung fibroblasts become activated (40) and produce excessive extracellular matrix (ECM) proteins, as well as various inflammatory and fibrotic mediators (3), resulting in the elevation of the levels of immune cells (41). Therefore, a two-pronged approach is deployed in the management of ILD in systemic sclerosis; controlling the extent of tissue fibrosis by using anti-fibrotic drugs, and curtailing excessive tissue injury (caused by the immune cells of the body) by employing immunosuppressant drugs (31).

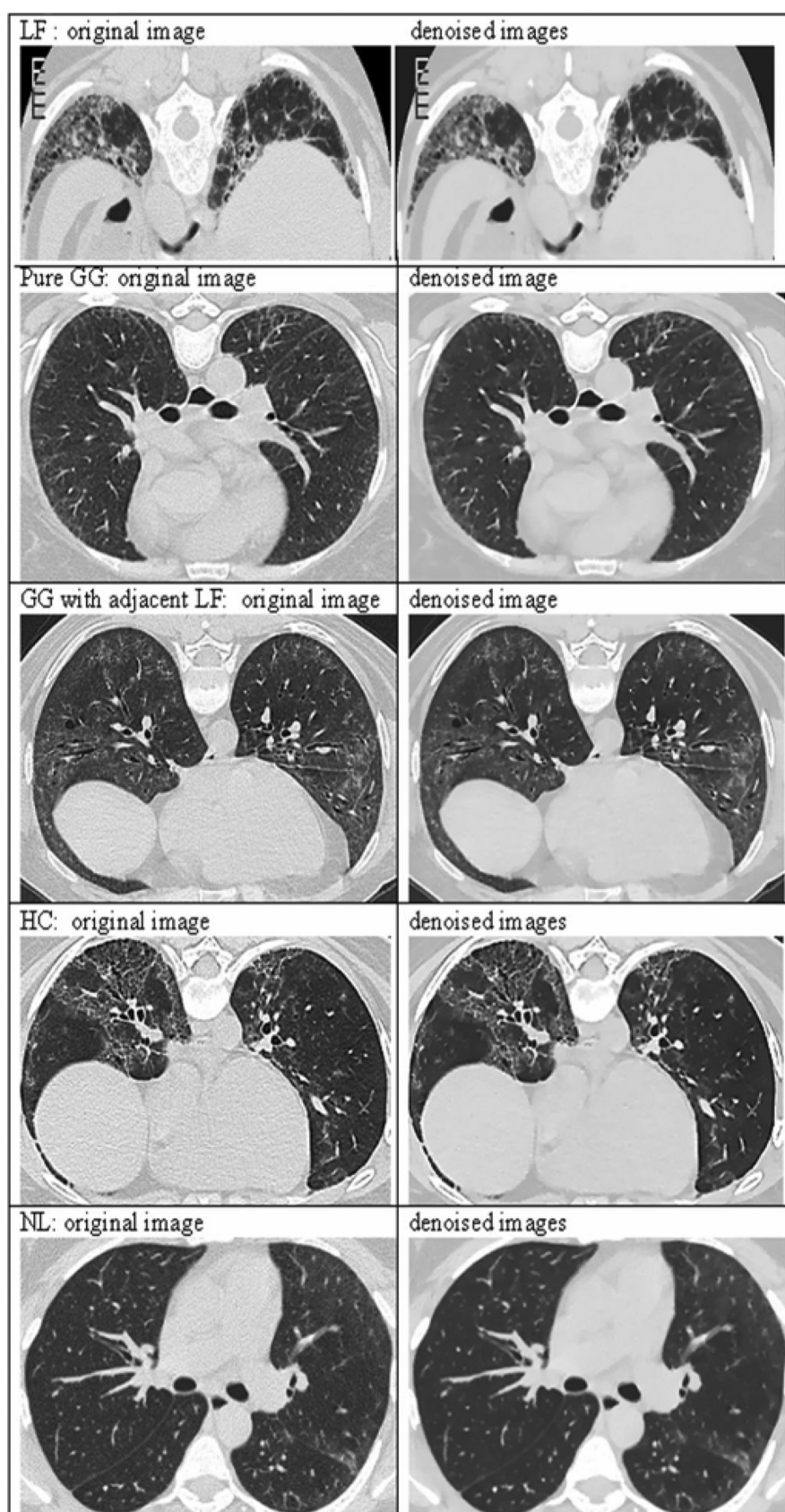
##### 5.1. Rituximab

Rituximab is a chimeric (of animal and human origin) monoclonal antibody normally employed in the treatment of cancer (42). It has been reported that patients with ILD in systemic sclerosis were successfully treated with

rituximab, when they did not respond to prednisolone and cyclophosphamide (43, 44). Since it is known that rituximab's mechanism of action is directed against the CD20 antigen on the surfaces of B lymphocytes (42), the study also reported the likelihood that B lymphocytes are implicated in the pathogenesis of the disease, further supporting previous studies which found elevated levels of B lymphocytes in lungs of patients with ILD in systemic sclerosis (45). The immune system is also implicated in the pathogenesis of ILD in systemic sclerosis, and so therapies targeted towards B cells and T cells might form plausible treatment consideration (46).

##### 5.2. Mycophenolate mofetil

Mycophenolate mofetil (MMF) is a derivative of a fungal antibiotic used to control organ transplant rejection (47). The use of it is reported to be safe and well-tolerated (48) in patients with ILD in systemic sclerosis (49), leading to improved lung function (50). The anti-fibrotic effects of MMF were also demonstrated in patients with ILD (51). It was also reported that MMF should be used, not as a first-line drug, but as a



**Fig. 2.** Normal CT scan images *versus* denoised CT scan images. A normal lung has a lower attenuation value compared to diseased ones. Copyright ©Elsevier. Reproduced with permission from Kim *et al.* Classification of parenchymal abnormality in scleroderma lung using a novel approach to denoise images collected via a multicenter study. *Acad Radiol* 2008; 15(8): 1004-16.

long-term immunosuppressive agent following treatment with intravenous cyclophosphamide (52). Another study also advocated the use of MMF with intravenous pulses of methylprednisolone and glucocorticoids in severe early systemic sclerosis (53). Furthermore, a large retrospective study at the Royal Free Hospital in the UK involving 100 patients demonstrated that MMF is very well-tolerated and appears to be at least as therapeutic as other drug regimens, warranting further evaluation in a randomised control trial (RCT) (54). In fact, the SLS II evaluates the effects of MMF to cyclophosphamide in a two-year RCT that is ongoing in the USA (NCT00883129) (55).

### 5.3. Imatinib

There is evidence that biologic agents might form a viable treatment consideration for ILD in systemic sclerosis (56). Tyrosine kinase inhibitors are a sub-class of biologics, and it has been suggested that they can be utilised as a therapeutic option (57). Imatinib (a biologic) is a tyrosine kinase inhibitor that can kill cancer cells (58). A study has shown that imatinib has anti-fibrotic effects, and it can also induce regression of established tissue fibrosis (59). However, the authors also acknowledged that there are no definitive conclusions regarding the safety and efficacy and hence, larger RCTs are needed. Despite this, there was also another study that demonstrated the combination of oral imatinib and intravenous cyclophosphamide was well-tolerated without major side effects, and patients also had improved lung function (60).

### 5.4. Methylprednisolone

Studies have outlined the therapeutic effects of using a combination of intravenous pulses of cyclophosphamide and methylprednisolone in patients with ILD in systemic sclerosis (61, 62). The investigators also highlighted the need for early diagnosis and treatment as those with an already severe functional impairment responded less well to treatment. In addition, they also advocated the notion that larger RCTs would have to be conducted in order to garner more evidence to establish

a more robust affirmation regarding treatment methods.

### 5.5. Cyclophosphamide

Perhaps the most widely used and studied treatment for early and severe ILD in systemic sclerosis is cyclophosphamide (52), although the costs and long-term therapeutic benefits still remain open to question (63). Cyclophosphamide is an alkylating agent that has immunomodulatory effects (64), and is often used in neoplastic diseases as well as rheumatoid arthritis (65). Its suppressive effects on lymphocytes also renders it a powerful immunosuppressant (66).

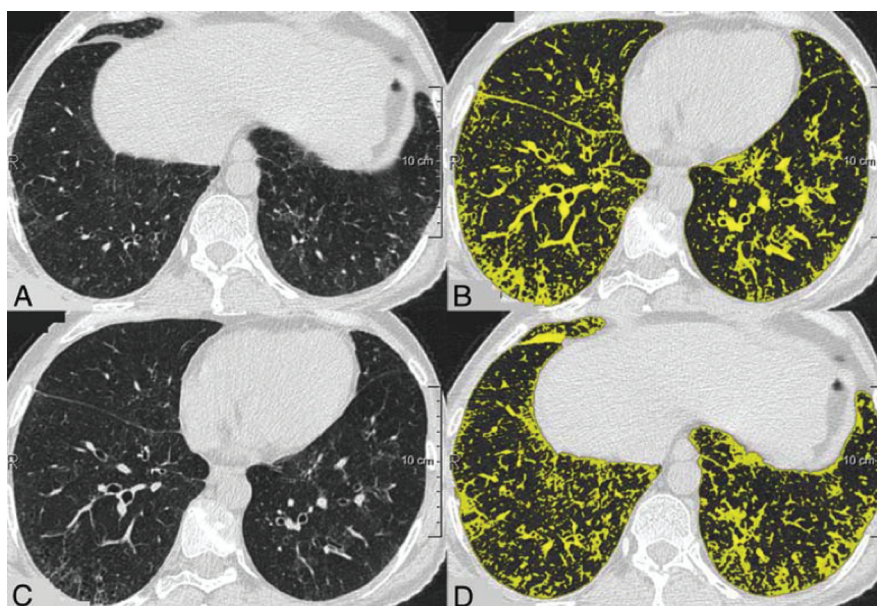
The Scleroderma Lung Study (SLS), a landmark and definitive 13-centre RCT involving 158 patients, was designed to evaluate the effectiveness and safety of oral cyclophosphamide for one year in patients with ILD in systemic sclerosis (67). Although results from the study demonstrated that cyclophosphamide alleviated breathing difficulties and improved patients' quality of life (67), the authors also admitted that it only had a modest therapeutic index. The therapeutic index of a drug is the measure of the maximum amount of drug that can be administered without causing excessive toxicity (68), and the formula for it is:

$$\text{Therapeutic index} = \frac{\text{Maximum non-toxic dose}}{\text{Minimum effective dose}}$$

Considering its immunosuppressive effects and bone marrow toxicity (65), a more effective therapy is needed for ILD in systemic sclerosis (69).

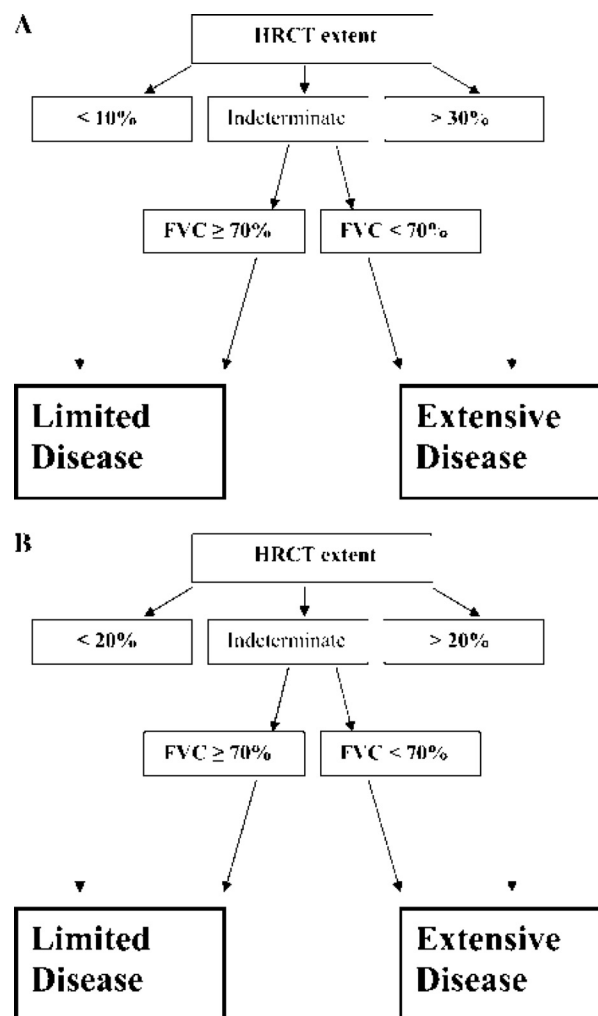
The SLS also showed that although the therapeutic effects of cyclophosphamide persisted for a few months after cessation of treatment, it was no longer apparent after 24 months (70). This was also corroborated by another study which showed the short-term (6 months) beneficial effects of cyclophosphamide (71).

In addition, another study indicated that patients' quality of life was actually reduced when given oral cyclophosphamide (72). The therapeutic effects of cyclophosphamide has also been called into question when a meta-analysis of 3 RCTs and 6 observational studies concluded that cyclophosphamide did not



**Fig. 3.** Normal CT scan images *versus* CAD CT scan images. Normal CT scan images showing a fibrotic lung (A, C). CAD allows clinicians to see the extent of fibrosis not normally detected by regular CT scans (B, D). Copyright ©Springer. Reproduced with permission from Marten K *et al.* Interstitial lung disease associated with collagen vascular disorders: disease quantification using a computer-aided diagnosis tool. *Eur Radiol* 2009; 19(2): 324-32.

**Fig. 4.** A simple staging algorithm. A flow chart that depicts the staging algorithm (A). Arbitrary values may differ slightly in clinical practice (B). Copyright ©American Thoracic Society. Reproduced with permission from Goh *et al.* Interstitial lung disease in systemic sclerosis: a simple staging system. *Am J Respir Crit Care Med* 2008; 177(11): 1248-54



result in any significant improvement of pulmonary function (73).

Nevertheless, there is strong evidence to suggest that cyclophosphamide reduces neutrophilic alveolitis in patients with ILD in systemic sclerosis (17). Corticosteroids are also sometimes used in conjunction with cyclophosphamide in treating ILD in systemic sclerosis (74). Mounting evidence demonstrates that a combination (75) of cyclophosphamide and prednisolone conferred a statistically significant respiratory improvement in patients (76). Azathioprine (an immunosuppressant) has also been found to be useful when given in combination with cyclophosphamide (77).

Furthermore, the Fibrosing Alveolitis in Scleroderma Trial (FAST), consisting of 45 patients using a combination of corticosteroids, cyclophosphamide and azathioprine, provides reason for optimism as it showed that there was improvement in the patients' forced vital capacity (FVC) with no increase in serious adverse events (78).

The European League Against Rheumatism (EULAR) Scleroderma Trials and Research group (EUSTAR) was conceived to develop evidence-based recommendations for the treatment of systemic sclerosis. Both EULAR and EUSTAR concluded that in view of the 2 (SLS and FAST) high-quality RCTs (67, 78), cyclophosphamide should be considered for use in the treatment of ILD in systemic sclerosis (79).

## 6. Advances in surgical considerations

Although drug treatments are generally used as a first-line defense against ILD in systemic sclerosis (52), the evidence supporting drug use in late-stage ILD is still lacking (43, 48, 50, 52, 59-61). A recent study reported that patients with the disease who received lung transplantation experienced similar rates of survival, as with patients with idiopathic pulmonary fibrosis and idiopathic pulmonary arterial hypertension (80). The study concluded that lung transplantation might well represent a viable therapeutic option to consider for patients with end-stage lung disease due to systemic sclerosis.

Another study also concluded that lung transplantation for patients with systemic sclerosis could well be a feasible option as it yielded good pulmonary function and acceptable morbidity and mortality (81).

## 7. Advances in cell-based therapy

Intense research is currently being done on the therapeutic effects of using stem cells in the realm of regenerative medicine. Therefore, it is not surprising that a number of published papers support the hypothesis that cell-based therapy can indeed be a treatment of choice in future for ILD in systemic sclerosis. A recent study concluded that bone marrow derived stem cells are important in the recovery of the lungs from injury, and that administering bone marrow derived mesenchymal stem cells (MSCs) can accelerate lung repair (82).

Another study also supported this hypothesis, stating that the MSCs differentiated into alveolar epithelial cells, and the transplanted cells curtailed lung injury and fibrosis (83). Although stem cells have the potential to differentiate into all cell types and are considered a valuable source of cells for transplantation therapies, a critical issue however, is the risk of tumour formation after transplantation (84).

In order to circumvent this problem, yet another study took a different approach to cell-based therapy, and transplanted alveolar type II cells instead (85). The study demonstrated the potential of intra-tracheal transplantation of alveolar type II cells, and it might well become a promising therapy for the future treatment of fibrotic lung diseases because these cells can be taken from patients' biopsy and cultured in the lab, thereby reducing the possibility of rejection.

## 8. Discussion

Although systemic sclerosis is a rare disease, and thus making ILD in systemic sclerosis rarer still, it is nevertheless a dreadful and debilitating affliction. Although there were many recent advances in the treatment of ILD in systemic sclerosis, the beneficial effects for most of them are modest and short-term. The Pulmonary Interstitial Vascular Organisational Task Force (PIVOT)

has concluded that there is significant variation in screening, diagnosis and treatment between rheumatologists and respiratory physicians (86), which suggests that specific designated centers have a role to play in standardising diagnosis and treatment methods in order to reduce heterogeneity which can confound meta-analyses. Furthermore, drug therapies are generally used in patients with early stage ILD in systemic sclerosis, and there is evidence that lung transplantation would be a viable option for late-stage patients, if not for the lack of donors. By virtue of its rarity in the population, even the highest of quality RCTs consisted of a small sample size of less than 200 patients, which would increase the standard error (SE) of the study (87). Also, due to the rare prevalence of ILD in systemic sclerosis, it would be essential to closely monitor and follow-up patients with this disease in order to better diagnose and manage new cases. This could be done by asking patients to fill up questionnaires on a regular basis in addition to routine assessments like measuring FVC.

## 9. Future directions

The advent of induced pluripotent stem (iPS) cells heralds a new beginning in the chapter of human cell biology (88). It is now a distinct possibility to study the iPS cell lines derived from patients with a specific disease of interest, and this could pave the way in elucidating the complex genetic variations and molecular pathways in humans. If this can be accomplished, then human models of human would have a dramatic effect on elucidating disease mechanisms (89).

The usefulness of an independent medication control officer (MCO), whose role is to maintain safety while retaining the blinding of the clinical trial, was assessed in the SLS. This is because drug toxicity from using cyclophosphamide is distinctively obvious to experienced clinicians, thus jeopardising the blinding of the trial. The study concluded that an MCO would be useful in preserving investigator-blinding, and might serve as a standard for future RCTs.

The reasons for the difficulty in studying ILD in systemic sclerosis are its low prevalence and the difficulty in correct-

ly diagnosing it. There is evidence to indicate that pulmonary hypertension can be closely associated with ILD, and so correctly identifying the two distinct entities are of paramount importance (90).

The PIVOT study calls for greater standardisation of screening, diagnostic techniques and treatment between rheumatologists and respiratory physicians. The 2 largest and highest quality studies so far (SLS in the US, and FAST in the UK) has provided much of the framework for which reviewers in EUSTAR and EULAR have recommended, and perhaps a joint collaboration between the investigators in the UK and USA would provide a more definitive solution in managing ILD in systemic sclerosis.

## 10. Conclusion

Despite the many hurdles faced and challenges which lie ahead, the advances made in the treatment and management of ILD in systemic sclerosis, however small, are very real. Until more RCTs are conducted with other treatment therapies, at the present moment, the reports and recommendations from EULAR and EUSTAR are convincing and authoritative for the treatment of ILD in systemic sclerosis.

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