

Pneumologia

Interstitial lung disease in systemic sclerosis: From immunopathogenesis to treatment

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Abstract

English:

Interstitial lung disease (ILD) is a pulmonary involvement that is commonly manifested in systemic sclerosis (SSc) patients. The immunopathogenesis of SSc-ILD involves several mechanisms, including microvascular injury, alveolar epithelial cell defect, inflammation, genetics, epigenetics, telomeres, telomerase and inflammasome, which result in lung fibrosis. Detection of ILD should be performed in every SSc patient by using high-resolution chest tomography (HRCT) scan of the thorax, in addition to evaluation by pulmonary function tests. When ILD is discovered, the physician might start treatment considering factors such as the extent of the lesion, progressivity of the disease, prognosis and drug toxicity. The current guideline recommends cyclophosphamide, mycophenolate mofetil and nintedanib as the initial choices for SSc-ILD treatment. Other agents such as biologic immunotherapies, haematopoietic stem cell transplantation and lung transplantation could be an option if the disease becomes progressive.

Keywords

inflammation • interstitial lung disease • nintedanib • lung fibrosis • systemic sclerosis

Pneumopatia interstițială difuză cu scleroză sistemică: De la imunopatogeneză la tratament

Rezumat

Romanian:

Pneumopatia interstițială difuză (PID) este o manifestare pulmonară frecventă la pacienții cu scleroză sistemică (SS). Imunopatogeneza PID din SS implică mai multe mecanisme, printre care injuria microvasculară, defectele epiteliului alveolar, inflamația, factori genetici, telomeri, telomerase și inflamazomul ce conduce la fibroză pulmonară. Identificarea PID trebuie făcută la toți pacienții cu SS prin tomografie computerizată cu înaltă rezoluție (HRCT) toracică și evaluare funcțională respiratorie. Când PID este identificată, tratamentul poate fi început ținând cont de extensia leziunilor, progresivitate, prognostic și toxicitatea medicamentoasă. Ghidurile actuale recomandă ciclofosfamidă, micofenolat mofetil și Nintedanib ca opțiuni inițiale pentru tratamentul PID-SS. Alți agenți, cum ar fi imunoterapiile biologice, transplantul de celule stem hematopoietice sau transplantul pulmonar pot fi luate în considerare dacă boala progresează.

Cuvinte-cheie

Inflamație • pneumopatie interstițială difuză • nintedanib • fibroză pulmonară • scleroză sistemică

Introduction

Systemic sclerosis (SSc) is a connective tissue disease that is characterised by three mechanisms: vasculopathy, which

is caused by endothelial dysfunction; augmented fibroblast activity resulting in progressive fibrosis; and autoimmunity.

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SSc may involve the skin and internal organs, including the lungs. Interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) are the major pulmonary involvements in SSc patients. Additionally, SSc can also affect the pleura or airways (1–5). When ILD occurs in patients with SSc, it contributes to poor prognosis such as worsening dyspnoea, exercise intolerance, respiratory failure and mortality. Early diagnosis and intervention may improve the clinical condition, lung function and quality of life of patients (4). In this review, we provide a discussion about the immunopathogenesis, diagnosis and current therapies for SSc-ILD.

Immunopathogenesis of SSc-ILD

The immunopathogenesis of SSc-ILD is characterised by microvascular injury, alveolar epithelial cell (AEC) defect and immune-mediated inflammation that results in collagen deposition and tissue fibrosis (Figure 1). Microvascular injury

and alveolitis appear in the early phase of SSc-ILD. One effect of vascular injury is the stimulation of a coagulation cascade that activates platelets and synthesises thrombin. Thrombin plays a role in producing pro-fibrotic cytokines, such as transforming growth factor (TGF)- β , connective tissue growth factor (CTGF) and interleukin (IL)-8, increasing endothelial permeability (which causes the migration of inflammatory cells through the endothelium) and inducing apoptosis in AEC. Furthermore, it promotes the differentiation of lung fibroblast into myofibroblast that is resistant to apoptosis. Thus, the accumulation of myofibroblasts leads to enhancing extracellular matrix (ECM) deposition, which is responsible for lung fibrosis. Another effect of microvascular injury is the release of endothelin (ET)-1 that may provoke fibrosis directly by binding to ET_A and ET_B receptors or indirectly through the actions of TGF- β (6–9).

Epithelial cell injury that is triggered by environmental insults may alter epithelial cells to mesenchymal cells, and this transformation process is known as an epithelial–mesenchymal transition (EMT). Mesenchymal cells gain

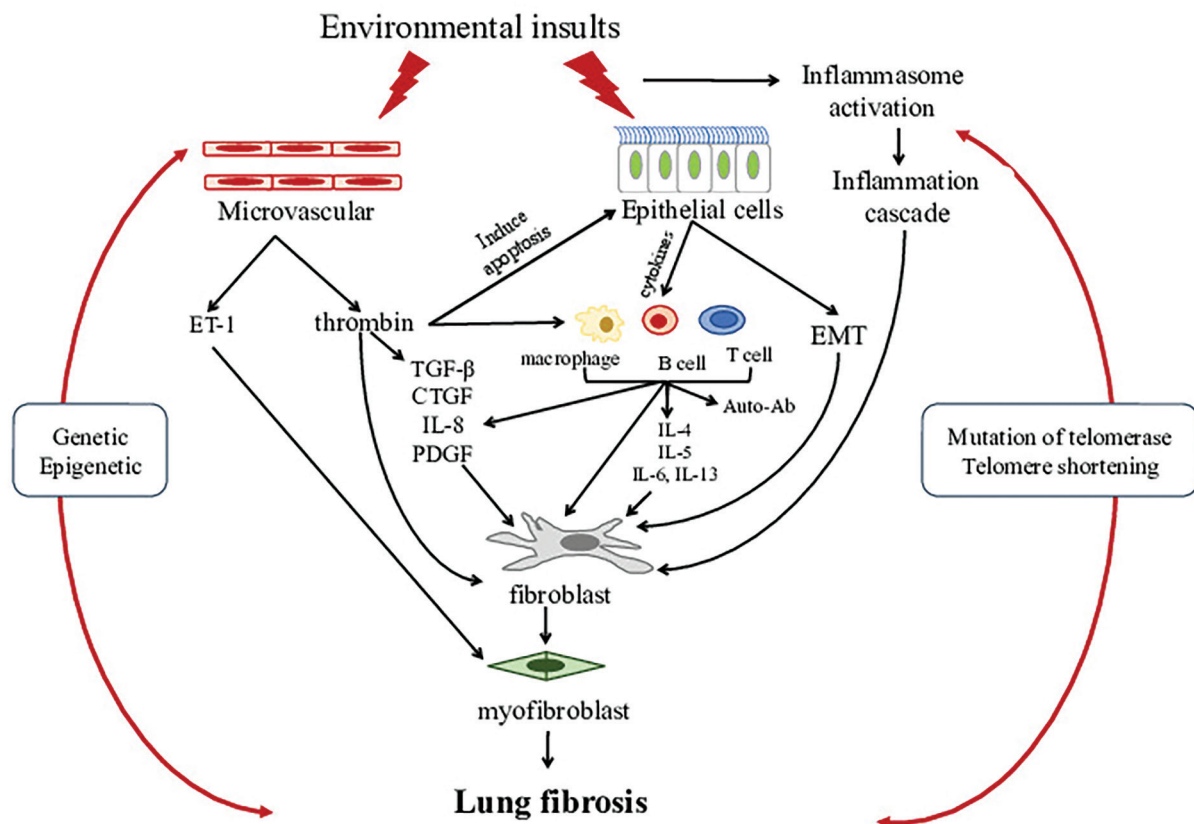


Figure 1. Immunopathogenesis of SSc-ILD. Ab, antibody; CTGF, connective tissue growth factor; EMT, epithelial–mesenchymal transition; ET, endothelin; IL, interleukin; ILD, interstitial lung disease; PDGF, platelet-derived growth factor; SSc, systemic sclerosis; TGF, transforming growth factor.

migratory capacity and apoptosis resistance, in addition to enhancement of ECM production. Moreover, the injured epithelial cells also generate various cytokines, which recruit inflammatory cells (7,8).

The role of inflammatory cells and cytokines in SSc-ILD was confirmed by the existence of lymphocytes, macrophages, neutrophils, eosinophils, TGF- β , CTGF, platelet-derived growth factor (PDGF) and IL-8 in the broncho-alveolar lavage (BAL) fluid. The predominance of T-cells varies in the organ tissues of SSc patients. In the lung, cluster of differentiation (CD)-8+ T-cells are greater in number than CD4+ T-cells. By comparison, CD4+ T-cells are the predominant T-cells in the skin of SSc patients. These cells enhance the secretion of IL-4, IL-5 and IL-6. Furthermore, IL-4 activates fibroblast proliferation, expression of adhesion molecules, chemotaxis and collagen synthesis, while IL-6 accompanies IL-4 to differentiate T-helper (Th)-2 cells and to extinguish interferon- γ to block Th-1 reaction that causes the activation of B-cells and fibroblast production (6,7).

The dysbalance of B-cell homeostasis in SSc-ILD may affect B-cell function. The enhancement of B-cell activation and the hyperreactivity of memory B-cells increase the production of cytokines, which in turn induces fibrosis and also releases several autoantibodies (auto-Abs). For instance, anti-topoisomerase or anti-Scl-70 has a strong correlation with the presence of ILD in 20%–40% of diffuse cutaneous (dc) SSc. Another auto-Ab is anti-Th/To ribonucleoprotein, which is frequently detected in limited cutaneous (lc) SSc-ILD. In contrast, an anti-centromere antibody that is also related to lc-SSc unusually appears in SSc-ILD. B-cells also regulate T-cell activation and differentiation by promoting Th-2 cells (5,6,10–14).

Another cell that plays a crucial function in SSc-ILD is the macrophage. After differentiation from monocytes, macrophages polarise into two phenotypes. The first phenotype is the classically activated (M1) macrophage, which are effector phagocytes and generate pro-inflammatory cytokines such as tumour necrosis factor (TNF)- α , IL-1 and IL-6. The other phenotype is the alternatively activated (M2) macrophage, which releases anti-inflammatory cytokines, including IL-4, IL-13 and IL-10. In addition, M1 macrophages trigger inflammation and tissue damage, while M2 macrophages induce Th-2 activities and tissue fibrosis (10). A recent study has revealed that the percentage of circulating mixed M1/M2 cells is higher in SSc patients than in healthy subjects (15). Additionally, a study by Trombetta et al. (16) concluded that the high proportion of circulating mixed M1/M2 cells in SSc patients has a significant relationship with the occurrence of ILD, systolic pulmonary artery pressure and anti-Scl-70 positivity.

Certain cytokines contribute to the pathogenesis of SSc-ILD. For example, TGF- β , which is released by fibroblasts,

endothelial cells and macrophages, stimulates the production of ECM and provokes fibroblast proliferation. Another cytokine is CTGF, which is synthesised by fibroblasts under the promotion of TGF- β . The expression of CTGF increases the stimulation of ECM proteins such as collagen and fibronectin and modulates the proliferation of fibroblasts. PDGF is a mediator that influences the production of ECM components, profibrotic chemokines and fibroblasts. Other mediators that also take part in fibrogenesis are monocyte chemoattractant protein (MCP)-1, insulin-like growth factor (IGF)-1, IL-18, TNF- α and various chemokines (6,7).

Newer concepts of pathogenesis of SSc-ILD are related to genetics, epigenetics, telomeres, telomerase and inflammasome. Many studies have demonstrated that positive family history of SSc would raise the risk about 15-fold in siblings or first-degree relatives. Both human leucocyte antigen (HLA)-dependent and non-HLA genes are associated with the occurrence of ILD in SSc patients. HLA-dependent genes that are linked with pulmonary fibrosis in SSc vary in different geographic locations and ethnicities. For instance, genes of the major histocompatibility complex (MHC) class II subtypes DP and DR influence SSc-ILD in South African and Korean patients, whereas European subjects may be affected by subtype DR only. MHC class I genes are primarily found in Caucasian subjects of SSc-ILD. On the other hand, non-HLA genes have been also detected in SSc-ILD-such as polymorphism in interferon regulatory factor (IRF)-5, matrix metalloproteinase (MMP)-12 and signal transducer and activator of transcription (STAT)-4 (8,9,17).

The mechanism of epigenetics also determines pulmonary fibrosis in SSc. Deoxyribonucleic acid (DNA) methylation inhibits the transcription process in the collagen suppressor gene FLI-1. Consequently, collagen synthesis dramatically increases and leads to pulmonary fibrosis. Another mechanism is histone acetylation, which modifies the structure of chromatin and induces a fibrotic process. Mutation of telomerase genes and telomere shortening may cause lung fibrosis in SSc. One hypothesis is that short telomeres interfere with the response of injured cells and render abnormal healing activity, thus developing tissue fibrosis. Furthermore, inflammasome also plays a role in fibrosis by activating pro-IL-1 β into IL-1 β and initiating the inflammatory cascade. This inflammation is followed by a repair process that results in fibroblast action (8,12,17).

Diagnosis and assessment

ILD assessments in SSc patients consist of respiratory symptoms, physical examination, chest imaging by high-resolution computed tomography (HRCT) and pulmonary

function tests (PFTs) (18,19). Among SSc-ILD patients, respiratory symptoms appear in around 25% of cases, PFT abnormality is seen in 40%–75% cases and HRCT could detect ILD patterns in just >90% of cases. Respiratory symptoms that may develop in SSc-ILD are dry cough, dyspnoea and fatigue, but patients can be asymptomatic at an early stage. On physical examination, the physician may hear bilateral basal crackles on chest auscultation (2,18–22). HRCT of the thorax is mandatory for the diagnosis of SSc-ILD. The most common pattern is non-specific interstitial pneumonia (NSIP), followed by usual interstitial pneumonia (UIP). Additionally, a study conducted by Bonifazi et al. (23) demonstrated that pleuroparenchymal fibro-elastosis is found in 18% of SSc-ILD patients. HRCT in SSc-ILD also often shows mediastinal lymphadenopathy, which is a reactive process resulting from inflammation or reflux. Nevertheless, it is also associated with other diseases such as sarcoidosis, tuberculosis or lymphoma (2,18–21,23).

The PFTs that can be performed in SSc-ILD patients are forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLCO). Although PFTs in SSc-ILD patients reveal restrictive patterns in spirometry and/or reduction in DLCO level, the result may be normal at an early stage. In contrast, several disorder-related SSc also impairs PFTs. For instance, pleural involvement, respiratory muscle weakness due to myositis and wide chest cutaneous disorder decrease the percentage of predicted FVC (%FVC), while emphysema and pulmonary vascular disease may reduce the percentage of predicted DLCO (%DLCO) (2,18–20). In contrast, with idiopathic ILD, lung biopsy and BAL should not be performed in SSc-ILD unless there are some indications. For example, the feature of ILD is atypical or other lung diseases also occur besides ILD, such as infection, granulomatous disease or malignancy (18,19).

Some experts recommend the protocol for SSc-ILD screening and monitoring. At first, after patients with SSc have been examined by HRCT and PFTs, they are grouped based on the presence of ILD. Afterwards, PFTs are done every 1–2 years in a patient without ILD, whereas in the ILD group, PFTs are conducted every 6 months regularly. If the decreasing level of FVC and DLCO is concordant, the patient should be evaluated by HRCT to ensure the progressivity of the disease (Figure 2) (2,19–21). Both FVC and DLCO should be performed to monitor ILD progression and their changes are significant when the reduction is $\geq 8\%$ in FVC and $\geq 13\%$ in DLCO (19).

Treatment

The decision to start the treatment for SSc-ILD considers several factors, including the progressivity of the disease,

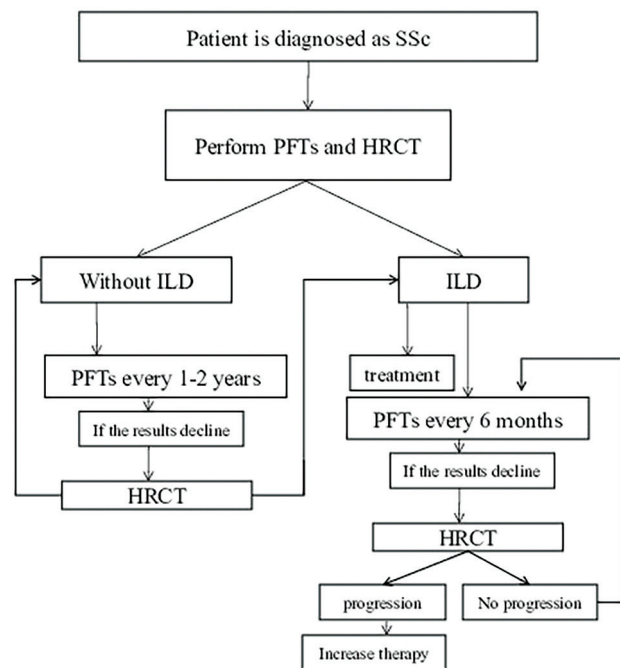


Figure 2. The protocol for screening and monitoring SSc-ILD. HRCT, high-resolution computed tomography; ILD, interstitial lung disease; PFT, pulmonary function test; SSc, systemic sclerosis.

prognosis and medication toxicity. Risk factors of worse prognosis are extensive lung disease, male gender, elderly status, decline of FVC at an early stage or DLCO level, co-existence of PAH or gastro-oesophageal reflux disease (GERD) and high level of C-reactive protein (CRP) at baseline (1,2,20,21). An algorithm has been proposed to diagnose the severity of the disease and to predict which patients are at higher risk of death. Abnormalities of >30% in HRCT are associated with extensive disease, while occupied area $\leq 10\%$ is defined as a limited disease. If the features of HRCT are unconvincing, extensive lung disease is concluded in patients with FVC <70% predicted (24). SSc-ILD patients in extensive disease groups are considered to receive pharmacologic treatment, whereas the limited disease group requires close monitoring (25).

The goals of SSc-ILD treatment are controlling inflammation and avoiding further fibrosis (4,7). In 2020, the *European Consensus for SSc-ILD Management* stated that mycophenolate mofetil (MMF), cyclophosphamide (CYC) and nintedanib could be used as treatment initiation for SSc-ILD. When the treatment response is inadequate or if the disease progresses, modifying the dose or choice of initial treatment, escalating treatment with other agents such as rituximab, haematopoietic stem-cell transplantation (HSCT)

Table 1. Drug of choice for SSc-ILD treatment.

Initial treatment	Escalation therapy
MMF	Modify dose or choice of MMF, CYC, nintedanib
CYC	Consider rituximab
Nintedanib (monotherapy or combination with MMF)	Evaluate for lung transplant Consider autologous HSCT for selected patients

CYC, cyclophosphamide; HSCT, haematopoietic stem-cell transplantation; MMF, mycophenolate mofetil.

and lung transplantation may be considered as options (Table 1) (25).

Non-specific immune suppression agents

CYC is an alkylating agent that represses lymphokine production and regulates lymphocyte function in suppressing the inflammatory response (7). Two randomised placebo-controlled trials demonstrated the efficacy of CYC in SSc-ILD. The first study is the Scleroderma Lung Study (SLS) I, which compared SSc-ILD patients who received either daily oral CYC (≤ 2 mg/kg) or placebo for 12 months. For the primary endpoints, this study noted that oral CYC increased %FVC, but there was no prominent effect on %DLCO. For secondary endpoints, CYC improved the dyspnoea index, percentage of total lung capacity (TLC), quality of life, skin thickness and radiographic extent of lung fibrosis. In follow-up observation, there was no significant difference between the two groups 12 months after CYC was discontinued. On the other hand, the adverse effects related to CYC that appeared in this trial were increasing infection, cancer, infertility and haematologic toxic effect (26,27).

The next trial was Fibrosing Alveolitis in Scleroderma Trial (FAST), which was conducted among 45 participants, who were randomised and divided into two groups. The treatment group received oral prednisolone (20 mg) on alternate days and infusions of CYC (600 mg/m²) every 4 weeks during a 6-months period, followed by oral azathioprine (AZA) (2.5 mg/kg/day) as maintenance therapy, whereas the control group received placebo. The result did not show a significant difference in both groups not only for primary outcomes (including %FVC and %DLCO) but also for secondary outcomes (such as HRCT appearance and dyspnoea score). However, it revealed that infusion CYC is well tolerated and there was no serious adverse effect that emerged during the investigation period (28).

MMF is an immunosuppressive agent that has a favourable safety profile for the treatment of autoimmune disorders and in the post-solid-organ transplantation state. It is an

inhibitor of inosine monophosphate dehydrogenase, which produces the DNA of both B- and T-cells. Hence, MMF suppresses the growth of those cells (29). The role of MMF in SSc-ILD has been observed in the SLS II, which was a multi-centre, double-blind randomised controlled trial (RCT). This study compared continuous 24 months of MMF administration (target dose: 1500 mg twice daily) with 12 months of oral CYC (target dose: 2 mg/kg/day) followed by 12 months of placebo and reported that both MMF and CYC increased %FVC from baseline to 24 months of treatment. Both agents also improved dyspnoea scores, HRCT appearance and skin thickness. In contrast, the MMF group showed less decline of %DLCO than the CYC group. The adverse effects that caused treatment withdrawal in the MMF group were fewer than in the CYC group, so MMF is not inferior to CYC for SSc-ILD treatment (27,30). A study by Baqir et al. (31) analysed 46 MMF-treated SSc-ILD patients for at least 12 months, with the majority being on 2 g daily. The study revealed that MMF stabilised %FVC, %DLCO, right ventricular systolic pressure predicted and %LD on HRCT (31).

Anti-fibrotic agents

The role of anti-fibrotic agents in the treatment of SSc-ILD is still being explored. Two agents that might be used for SSc-ILD are nintedanib and pirfenidone. Nintedanib is a tyrosine kinase receptor antagonist, which acts in inhibiting the proliferation, migration and differentiation of fibroblasts, as well as inhibiting ECM secretion. Distler et al. (32) conducted the Safety and Efficacy of Nintedanib in Systemic Sclerosis (SENSCIS) trial, which was a randomised, double-blind, placebo-controlled trial in 32 countries. This study aimed to investigate the efficacy and safety of nintedanib in SScILD patients. A total of 576 SSc-ILD patients were recruited in this study, where the treatment group received 150 mg of nintedanib twice daily and another group received a placebo. About half of the participants were receiving MMF as the baseline therapy. They discovered that the rate of decline in FVC was lower in the treatment group than in the placebo group at 52 weeks (-52.4 mL vs -93.3 mL) (27,32).

On the other hand, the effect of pirfenidone in SSc-ILD is still unsatisfactory. The mechanism of action of pirfenidone has not been elucidated. It plays a role in suppressing the proliferation of fibroblasts, inhibiting pro-inflammatory and pro-fibrotic cytokines and decreasing collagen production (33). Acharya et al. conducted a double-blind RCT among 34 subjects of SSc-ILD. This study failed to show an effect of pirfenidone for stabilisation in %FVC (34). Another study was the An Open Label, RandOmized, Phase 2 STUdy of the Safety and Tolerability of Pirfenidone when Administered

to Patients with Systemic Sclerosis-Related Interstitial Lung Disease (LOTUSS) trial, which was a phase II study that assessed the safety and tolerability of pirfenidone in SSc-ILD patients. It showed that this agent is well tolerated, and better tolerability was achieved when pirfenidone was given in a longer titration (35). Another study of pirfenidone, namely SLS III, is still ongoing, which examines the efficacy of pirfenidone versus placebo in SSc-ILD patients who are administered MMF (1).

Biologic immunotherapies

Rituximab (RTX) is a monoclonal Ab directed against the CD20 antigen that depletes B-cells from circulation. Jordan et al. (13) performed a nested case-control study that evaluated the effect of RTX on the lung function of SSc-ILD patients as the secondary objective of this study. They found that %FVC was stable and %DLCO was improved significantly in RTX-treated patients at 6 months of follow-up (13). Additionally, it noted that %FVC rose in the RTX group compared with the control group. Sircar et al. (37) conducted an RCT to compare the efficacy and safety of RTX versus CYC. They discovered that the %FVC in the RTX group increased from 61.3% to 67.5%, while it dropped from 59.2% to 58.1% in the CYC group. Moreover, there were no serious adverse events, such as malignancy, leucopenia, gangrene or ovarian failure, appearing in the RTX group (36).

Tocilizumab (TCZ) is a monoclonal Ab against IL-6. The efficacy and safety of TCZ for SSc-ILD were exhibited by the faSScinate Trial, which was a double-blind RCT conducted among progressive SSc patients with ≤ 5 -years duration of the disease. In phase I, the TCZ group received a weekly subcutaneous injection of TCZ 162 mg, compared with the placebo group, and was observed for 48 weeks. The result showed that the change of FVC was -117 mL from the baseline in the TCZ group versus -237 mL in the placebo group. The proportion of subjects with reduction of >10% predicted in FVC was 10% in the TCZ group and 23% in the placebo group (37). In phase II, both groups in phase I received a weekly subcutaneous injection of TCZ 162 mg for the next 48 weeks. None of the subjects from the two groups experienced >10% decline of %FVC at 96 weeks. In addition, this study noted that infection was the most common adverse event that occurred after TCZ was used (38).

Another study by Narváez et al. (39) in nine patients with worsening SSc-ILD who were treated with intravenous or subcutaneous injection of TCZ for at least 6 months revealed that pulmonary function was improved or stabilised in 44% of subjects. However, five patients discontinued TCZ, which was

related to serious adverse events, inefficacy and progressing ILD (39).

HSCT in SSc-ILD

HSCT is an alternative therapeutic option that is considered for SSc-ILD patients with rapidly progressive disease who have been refractory to other treatments. The Autologous Stem Cell Transplantation International Scleroderma (ASTIS) trial compared the efficacy of autologous HSCT with intravenous pulse CYC for dc-SSc patients accompanied by lungs, heart or kidney involvements. It demonstrated that the HSCT arm had better long-term survival and significant improvement in lung function than the CYC arm. Therefore, HSCT treatment was linked to early death (40). Another study is the Scleroderma Cyclophosphamide or Transplantation (SCOT) trial, which compared myelo-ablative therapy and CD-34⁺ autologous HSCT versus CYC for severe SSc with internal organ involvements, including ILD. The result showed that the myelo-ablative autologous HSCT group had a greater rate of event-free survival than the CYC group at 54 months and 72 months (41).

Lung transplantation

Lung transplantation is an option for SSc-ILD patients who have not responded to treatment, and it can be performed in patients who do not have accompanying extra-pulmonary complications, such as oesophageal dysmotility, malnutrition and renal disease. Chan et al. (42) observed and compared 5 years of survival between SSc with ILD or PAH and non-SSc with restrictive lung disease patients who underwent a bilateral lung transplant. This study demonstrated that survival rates at 1 year and 5 years were not significantly different between the two groups (42). Pradère et al. investigated survival rates among 90 SSc patients with ILD, pulmonary hypertension (PH)-ILD or PAH, who received a lung transplant at 14 centres. They found that the survival rates at 1, 3 and 5 years were 81%, 68% and 61% respectively. A high risk of death was associated with the female gender and occurrence of PAH (43).

In summary, the immunopathogenesis of SSc-ILD is a complex process that involves microvascular injury, epithelial cell defect, the contribution of inflammatory cells and cytokines, genetics, epigenetics, telomeres, telomerase and inflammasome. ILD should be screened for in SSc patients although it is asymptomatic. Chest HRCT is mandatory in ILD diagnosis, while PFTs play a role in ILD evaluation. SSc-ILD patients who are categorised as an extensive lung disease group should be treated. Nowadays, the first line of SSc-ILD treatment is not only immunosuppressant drugs but also anti-fibrotic agents. However, modifying the initial therapy or using

other alternative treatments, such as biological agents, HSCT or lung transplants, could be used as the escalating therapy option.

Author contribution

Amanda G: conception, writing, reviewing, and endorsement of the final version. Sutoyo DK: conception, writing, reviewing, and endorsement of the final version.

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Conflict of interest

No potential conflict of interest relevant to this article was reported.

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