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REVIEW

Management of systemic sclerosis associated with interstitial lung disease

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Abstract

Systemic sclerosis (SSc) is a rare connective tissue disease characterized by immune dysregulation, microangiopathy and fibrosis that affects the skin and multiple internal organs, including the lung. Interstitial lung disease (ILD) is prevalent in up to 50% of SSc patients and is a leading cause of morbidity and mortality. Over the last decade there have been significant advances in the diagnosis, monitoring, and treatment of SSc-associated ILD (SSc-ILD). Current treatment options for SSc-ILD include conventional and biologic immunosuppressive therapies and antifibrotic agents. Other interventions, such as autologous hematopoietic stem cell transplant (AHSCT) and lung transplantation are reserved for severe refractory cases. Multidisciplinary management provides the best care for SSc-ILD patients. In clinical practice treatment should be individualized based on factors such as SSc phenotype, ILD severity, risk factors for progression, evidence of progression, comorbidities, and preference of patients. This paper provides an overview of the current perspectives on management of patients with SSc-ILD.

Keywords: interstitial lung disease, systemic sclerosis, immunosuppressive treatment, antifibrotic therapy, autologous hematopoietic stem cell transplant.

Introduction

Systemic sclerosis (SSc) is a rare systemic autoimmune disease that affects skin, blood vessels, musculoskeletal system, and internal organs including the lung, gastrointestinal tract, heart, and kidney. SSc pathogenesis is known only partially and includes three key pathophysiological processes: 1). vascular injury characterized by endothelial wall damage and fibro-proliferative vasculopathy; 2). immunological dysregulation of the innate and acquired immune system; 3). fibrosis of the skin and internal organs. Clinical manifestations and disease progression are due to a complex interplay between these pathologic processes in various organs. At present, the accepted hypothesis is that the complex immune-inflammatory dysregulation triggered by genetic and environmental factors is a key mechanism in initiation and progression toward structural vasculopathy and progressive fibrosis [1].

SSc is a heterogenous disease, with high variability in clinical presentation, antibodies profile, and disease progression. Traditionally, according to criteria of Le Roy et al. [2], SSc has been divided into two major phenotypes based on the extension of skin involvement: diffuse cutaneous SSc (dcSSc) characterized by involvement of the skin proximally to the elbows and knees, including the trunk, and limited cutaneous SSc (lcSSc) characterized by involvement of the skin distally to the elbows and knees. Identification of these clinical subsets of SSc is important as they have prognostic value to stratify patients for disease complications and treatment strategy. Studies have shown that dcSSc is associated with anti-topoisomerase I antibodies (ATA), interstitial lung disease (ILD) and poor prognosis, while lcSSc is associated with anti-centromer antibodies, less organ involvement and better prognosis [3]. In clinical practice, other clinical subsets were identified, including SSc sine scleroderma (ssSSc) in which there is no skin involvement but internal organ fibrosis and typical antibodies [4], and overlap syndromes, such as scleromyositis [5]. The heterogenous spectrum of this disease poses challenges to predicting the development of organ involvement and targeting appropriate treatment in SSc patients [6]. In recent years, there has been a paradigm shift in how we understand and identify SSc subsets, based not only on the extent of skin involvement, but also on organ involvement, serologic profile, pathophysiologic phenotype predominance (vasculopathic, inflammatory, fibrotic), rate of progression and prognosis [3,7].

Diagnosis and monitoring of SSc-ILD

SSc-associated ILD (SSc-ILD) is one of the most severe complications and is the leading cause of morbidity and mortality in SSc patients [8]. Currently, SSc-ILD is associated with a 10-year mortality of up to 40% [9]. Moreover, SSc-ILD is associated with reduced health-related quality of life [10]. Epidemiologic studies showed a large variability in the reported prevalence and incidence of SSc-ILD, with significant geographical heterogeneity. ILD affects approximately 50% of SSc patients [11]. Among 3656 patients in the European Scleroderma Trials and Research group (EUSTAR), ILD was present in 53% of dcSSc and 35% lcSSc patients [12]. Risk factors for the development of ILD include anti-topoisomearase I positivity, dcSSC subset, smoking history, male gender, older age, African American ethnicity [13].

During the early stages of ILD patients can be asymptomatic. As the disease progresses, patients present exertional dyspnea, dry cough, and fatigability. An important clinical sign is the presence of "velcro-type" crakles at the bases of the lungs [14]. Many experts recommend that all patients with SSc should be screened at baseline for ILD using high-resolution computed tomography (HRCT). In addition, pulmonary function tests (PFTs) should be performed at baseline and at regular follow-up intervals [15]. Fibrotic nonspecific interstitial pneumonia (NSIP) is the most common pattern of ILD, present in two-thirds of SSc patients, followed by usual interstitial pneumonia (UIP). NSIP is characterized by varying degrees of inflammation and fibrosis, with some forms being predominantly inflammatory (cellular NSIP) and the most forms being primarily fibrotic (fibrotic NSIP). Occasionally, patients with NSIP may present coexisting organizing pneumonia. On HRCT, the NSIP pattern is defined by the presence of ground-glass opacities in a peripheral distribution with subpleural and basilar predominance. In fibrotic NSIP, common findings are reticular pattern, traction bronchiectasis and volume loss. The UIP pattern is characterized by the presence of honeycombing, reticular pattern, volume loss, with minimal ground-glass opacities [14]. In contrast to idiopathic ILD, no significant difference in survival between different histopathological subtypes of ILD was observed in SSc patients [16].

HRCT and PFTs are also used for the assessment of ILD severity and monitoring and have prognostic value. Extensive lung disease classified as more than 20% abnormalities on HRCT is associated with a more rapid decline of lung function and high mortality in SSc patients. When HRCT evaluation is inconclusive (lung abnormalities between 10-30%), patients with forced-vital capacity (FVC) less than 70% predicted are considered to have extensive disease [17]. SSc-ILD usually occurs in the first 3-5 years of evolution, but recent data from EUSTAR registry showed that ILD progression can appear at any disease duration. Given this high heterogeneity and variability of the ILD course in SSc, all patients should be monitored regularly to assess disease progression and guide therapeutic decisions [18].

Evidence from observational studies suggests that approximately 20-30% of patients with SSc-ILD will have a progressive disease course, while 50% remains stable, and some patients experience improvement of lung function. Most patients showed both periods of progression and stable/improvement periods [19]. Progressive pulmonary fibrosis is a phenotype of ILD characterized by fibrosis on HRCT imaging and evidence of progression over time [20]. Risk factors for development of progressive phenotype in SSc-ILD patients include older age, male gender, smoking history, anti-topoisomearase I positivity, dcSSC subset, high modified Rodnan skin score (mRSS), arthritis, gastroesophageal reflux, lower SpO2 after a 6-min walk test (6MWT), extent of fibrosis on HRCT ($\geq$ 20%), low baseline FVC and diffusing capacity of the lung for carbon monoxide (DLCO). Different definitions for ILD progression have been proposed. Based on clinical trials, the most frequently used definition of ILD progression is a relative decline in FVC of $\geq$10%, or 5–9% plus a decline in DLCO $\geq$15%. Longitudinal management in patients with ILD or risk factors for progressive ILD should include serial measurements of FVC and DLCO, typically every 3-6 months. Also, an increase of the extent of ILD on follow-up HRCT is considered a marker of disease progression. The most recent clinical practice guideline defined progressive pulmonary fibrosis based on the presence of at least two of the following three criteria occurring within 1 year: worsening of respiratory symptoms, decline of lung function (absolute decline in FVC of at least 5% predicted or/and absolute decline of DLCO at least 10% predicted) and radiologic evidence of increased extent of fibrosis [21]. It is of paramount importance to identify patients with progressive pulmonary fibrosis, as this phenotype is associated with increased mortality risk [13].

Treatment options of SSc-ILD

Recent advances in the field of SSc and ILD have provided new insights and developments of new therapies. Several effective therapeutic options are used in clinical practice for the treatment of SSc-ILD, including conventional disease-modifying antirheumatic drugs (cDMARDs), biologic DMARDs (bDMARDs) and antifibrotic agents.

Cyclophosphamide has been the gold standard for treatment of severe progressive SSc and SSc-ILD for many years [22]. New evidence from cohort-studies and placebo-controlled randomized controlled trials (RCTs) support the efficacy and safety of immunosupression with mycophenolate mofetil, tocilizumab and rituximab, and of antifibrotic treatment with nintedanib. In severe cases of refractory SSc-ILD, autologous hematopoietic stem cell transplant and lung transplantation can be considered. Additional supportive interventions are recommended including treatment of

gastroesophageal reflux, smoking cessation, pulmonary rehabilitation, oxygen therapy, prophylaxis of infections and treatment of concomitant pulmonary hypertension [23].

Immunosuppressive treatment

Studies indicate that treatment with both conventional immunomodulatory drugs and biological agents results in better outcome for SSc-ILD patients. Therefore, immunosuppressive agents are considered the cornerstone of treatment in SSc-ILD patients [24]. Currently, there are four immunosuppressive drugs used in clinical practice for the treatment of SSc-ILD: cyclophosphamide, mycophenolate mofetil, tocilizumab and rituximab.

Conventional DMARDs

cDMARDs has been used for a long time in clinical practice for patients with SSc-ILD. Cyclophosphamide and mycophenolate mofetil are most used in SSc-ILD and have been shown to preserve lung function [25]. Other cDMARDs may improve pulmonary function, such as methotrexate, but there are few data available.

Cyclophosphamide (CYC) is a cytotoxic alkylating agent used in the treatment of SSc-ILD for more than 25 years. Many observational studies showed efficacy of CYC for skin and lung manifestations in SSc patients [26]. The most robust evidence supporting its efficacy in SSc-ILD comes from RCTs. In The Scleroderma Lung Study (SLS I), patients were randomized to 12 months of oral CYC or placebo, and then followed another 12 months without therapy. In the study were included symptomatic patients with active alveolitis on bronchoalveolar lavage and ground glass opacities on HRCT. There was a statistically significant but clinically modest improvement of FVC% predicted (+ 2,53%, $p < 0.03$) in favor of CYC compared to placebo. In addition, there was a significant reduction of mRSS in CYC treated patients compared to placebo. Other favorable effects of CYC were observed on dyspnea and quality of life. There was no correlation between the presence of ground-glass opacities on HRCT and treatment response. However, the presence of severe fibrosis correlated with treatment response. Concerns about safety arose due to relatively common side effects in the CYC treated patients, including cytopenia, infections, and digestive intolerance. Long term use is associated with infertility and increased risk of malignancy [27]. Moreover, CYC had modest long-term benefits, with most improvements being lost by the 2-year follow-up [28]. These results suggest that the beneficial effect of CYC is confined to patients with extensive fibrotic disease and that ongoing immunosuppression is required to maintain the benefits of CYC. Being considered a potentially toxic medication, CYC use is time-limited to induction phase, and other immunosuppressive agents are needed in the maintenance phase, including azathioprine (AZA), MMF or methotrexate (MTX) [22]. The FAST (Fibrosing Alveolitis in Scleroderma Trial) trial had a similar design to the SLS I trial but investigated 6 months of intravenous CYC compared to placebo, followed by oral azathioprine. After 12 months, the benefits of this treatment were no different from placebo, although FVC showed a trend towards improvement in the treatment group compared with placebo group, that did not reach statistical significance. Also, there was no effect on dyspnea or fibrosis extent on imaging [29].

Mycophenolate mofetil (MMF) is an inhibitor of inosine monophosphate dehydrogenase, which inhibits lymphocyte proliferation and migration. In recent years it has become widely used for the treatment of many inflammatory diseases, including lupus nephritis and ILD [30]. Concerns regarding the side effects associated with CYC prompted the design of the SLS II trial which compared oral CYC with MMF for the treatment of SSc-ILD. In this trial, 142 patients with SSc-ILD were randomized to receive either MMF for two years or CYC for one year, followed by placebo for another year. While the trial didn't meet its primary endpoint of superiority of MMF over CYC, the change in FVC% predicted at 24 months was similar in MMF and CYC group. The results indicate that two years of MMF therapy provided similar benefits compared to one year of oral CYC in SSc-ILD patients. Clinically important was the observation that in the MMF arm were observed fewer patients who discontinued therapy and less adverse events in comparation with oral CYC arm [31]. Based on these results, MMF is considered an equally efficient but safer alternative to CYC in SSc-ILD and it is used as first line agent in many medical centers [32].

Biologic DMARDs

Biologic agents are widely used in rheumatology, and recently have been used with good clinical results for treatment of SSc-ILD. According to the expert guidelines, tocilizumab and rituximab are recommended as second-line agents in the treatment of SSc-ILD [32].

Tocilizumab (TCZ) is a humanised anti-IL-6 receptor monoclonal antibody approved for the treatment of early dcSSc, based on the results of two RCTs - the phase II faSScinate (Study of RoActemra/Actemra (Tocilizumab) Versus Placebo in Patients With Systemic Sclerosis) and phase III focuSSced (Study of the Efficacy and Safety of Tocilizumab in Participants with Systemic Sclerosis) trials [33,34]. The primary endpoint was the change from baseline to week 24 (faSScinate trial), respectively to week 48 (focuSSed trial) in mRSS, and was not met. However, both studies meet the secondary endpoint, which was the change between baseline and weeks 24 and 48 in FVC% predicted. The focuSSced trial, a multicentric RCT, enrolled 210 patients with early (less than 5 years from onset of the first non-Raynaud manifestation) dcSSc, with

progressive skin fibrosis and inflammatory phenotype (elevated levels of C-reactive protein) and mild baseline FVC% predicted deficit. Patients were randomized 1:1 to receive subcutaneous TCZ in monotherapy or placebo. Regarding the mRSS change from baseline to week 48, there was a numerical difference in favor of TCZ, but the difference was not statistically significant (mRSS change: -4.1 versus -6.1 in placebo and TCZ group, respectively, $p = 0.1$). In the TCZ arm the decline in FVC% predicted at week 48 was -0.4 compared to -4.6 in the placebo group ($p = 0.0002$). A more profound effect was observed in the subgroup analysis of patients with SSc-ILD: the change in FVC% predicted was -0.1 for TCZ and -6.3 for placebo ($p < 0.0001$). Moreover, TCZ showed benefits on lung fibrosis as assessed using quantitative HRCT. These results support the use of TCZ in patients with early SSc-ILD, with skin progressive and inflammatory phenotype. Based on the results of faSScinate and focuSSced trials, TCZ became the first biologic medication approved for treatment of SSc-ILD.

Rituximab (RTX) is chimeric anti-CD20 monoclonal antibody used for the treatment of rheumatoid arthritis, systemic vasculitis, lymphoma, and ILD associated with a wide range of connective tissue diseases (CTDs). RTX was used in SSc-ILD naïve patients, as well as in patients with SSc-ILD refractory to other immunosuppressive agents. Efficacy and safety of RTX in SSc was evaluated in two recent meta-analysis. Tang R et al [35], analysed 14 studies, including 597 patients with SSc treated with RTX, and showed stabilization of FVC and DLCO, as well as favorable effects on skin fibrosis. Another meta-analysis assessed the efficacy of RTX on the lung function parameters in SSc-ILD patients. This meta-analysis of 20 studies, including 575 SSc-ILD patients, demonstrated that treatment with RTX was associated with a significant improvement in both FVC and DLCO during the first year of treatment. In addition, analysis of five studies in which side effects were reported showed that RTX was associated with fewer adverse events, especially infectious ones, in comparation with controls [36]. Recently, there were two RCTs published and their results support the use of RTX in the treatment of SSc-ILD. The DESIRE (Safety and efficacy of rituximab in systemic sclerosis) trial, a multicentric RCT conducted in Japan, randomized 56 patients with SSc versus placebo and assess the effect of RTX on skin disease. At week 24, the mRSS was significantly improved In the RTX group compared to the placebo group (6.3 decrease in the RTX group versus 2.1 increase in the placebo group, $p < 0.0001$). In the subgroup analysis of SSc-ILD patients (48 patients) it was shown that FVC% predicted was significantly improved in patients treated with RTX (0.09% improvement in the rituximab group versus 2.87% decrease in the placebo group, $p = 0.04$). The frequency of adverse events were comparable in both groups [37]. In the RECITAL (Rituximab versus cyclophosphamide for the treatment of connective tissue disease-associated interstitial lung disease) trial, a multicentric UK study, patients with a wide range of CTDs (SSc, idiopathic inflammatory myositis, and mixed CTDs) and associated ILD (CTD-ILD) were randomized to receive RTX or CYC. At week 24, FVC was similarly improved in both groups (the unadjusted mean increase was 99 ml in the CYC group versus 97 ml in the RTX group). Moreover, improvement in the respiratory-related quality of life measures, overall survival and progressive-free survival did not significantly differ between the groups. RTX was associated with fewer adverse events and lower corticosteroid exposure in comparation with CYC [38]. The results of these studies suggest that RTX might be an effective and safe alternative to CYC in patients with severe and progressive CTD-ILD.

Antifibrotic treatment

Both antifibrotic agents, nintedanib and pirfenidone, approved for the treatment of idiopathic pulmonary fibrosis (IPF) have been tested in SSc-ILD, based on the common etiopathogenetic mechanisms hypothesis.

Nintedanib is an oral tyrosine kinase inhibitor with antifibrotic properties, licensed for use in the treatment of IPF patients, based on the results of INPULSIS-1 and INPULSIS-2 trials [39]. More recently, the SENSCIS (Safety and Efficacy of Nintedanib in Systemic Sclerosis) and INBUILD (Efficacy and Safety of Nintedanib in Patients with Progressive Fibrosing Interstitial Lung Disease) trials showed the efficacy of nintedanib in slowing the decline in pulmonary function in SSc-ILD and other chronic fibrotic ILD with progressive phenotype, respectively [40,41].

Based on the results of SENSCIS trial, nintedanib has been approved as a new treatment in patients with SSc-ILD. In this phase-3, multicentric, RCT study were enrolled 576 patients with SSc-ILD, with disease duration of less than 7 years and with HRCT showing fibrosis affecting at least 10% of the lungs. Participants were randomly assigned to receive either 150 mg of nintedanib twice daily or placebo for 52 weeks. The trial reached its primary end point with a rate of annual FVC decline reduced by 44% in the group receiving nintedanib (- 52.4 ml/year versus -93.3 ml/year; delta FVC of 41 ml/year). There was no significant difference between groups in the change in the skin score (mRSS) and health-related quality of life (assessed by St. George's Respiratory Questionnaire [SGRQ]). About half of the patients enrolled in the SENSCIS trial had the lcSSc phenotype, whereas previous studies included mainly patients with dcSSc. The rate of decline in FVC was higher in dcSSc patients than in lcSSc patients (-112.0 ml/year vs. -74.5 ml/year). Nearly half of the subjects from the SENSCIS trial were on stable dose of MMF at enrollment. The magnitude of the effect of nintedanib was slightly better in patients who were taking MMF than in patients who were not receiving MMF at baseline, but the difference was not

statistically significant. Thus, the SENSCIS cohort mirrors the heterogeneity of SSc, suggesting that the results are applicable in the entire spectrum of the disease [40].

Post-hoc analysis of the SENSCIS trial showed no heterogeneity in the effect of nintedanib on the rate of FVC decline across subgroups based on demographics, severity of ILD on HRCT, FVC thresholds at baseline, antibodies or use of DMARDs at baseline. In a subgroup analysis of the SENCIS trial, nintedanib reduced the ILD progression in both patients with and without MMF at baseline. Moreover, the adverse events profile of nintedanib was similar in both subgroups. It has been suggested that the combination of an antifibrotic and an immunosuppressive agent may enhance therapeutic efficacy against lung fibrosis, but further research are needed regarding the combination therapy with nintedanib and immunusupressors [42]. In another post-hoc analysis of SENCIS trial was found a small numeric difference in the effect of nintedanib on slowing the FVC decline over 52 weeks in favor of patients who had risk factors for progressive ILD, such as short disease duration, extensive skin involvement (high mRSS) and elevated inflammatory markers [43]. Denton et al. [44] showed that there were no differences in the effect of nintedanib depending on the extent of lung fibrosis on HRCT. Taken together, these findings suggest that the relative effect of nintedanib is similar across the spectrum of disease severity, and that patients could benefit from nintedanib irrespective of their baseline characteristics, including the severity of lung fibrosis [45].

In the open-label extension, SENSCIS-ON trial (A Trial to Evaluate the Safety of Long Term Treatment with Nintedanib in Patients with Scleroderma Related Lung Fibrosis), the effect of nintedanib on slowing the FVC decline was maintained over 100 weeks. Data from this study suggests that the efficacy and safety of nintedanib in SSc-ILD is similar over long-term use [46,47].

The adverse event profile of nintedanib in patients with SSc-ILD was similar to that observed in patients with IPF, being characterized mainly by gastrointestinal events. The most common adverse event was diarrhea, reported in 75% of patients treated with nintedanib, versus 31% in the placebo group. Other gastrointestinal adverse events, including nausea, vomiting, abdominal pain and weight loss were also more common in patients treated with nintedanib than placebo. However, gastrointestinal adverse events in the nintedanib-treated group were reported with similar frequency in SSc patients with and without a predisposition for gastrointestinal events. The low rate of permanent discontinuation of nintedanb due to diarrhea (6.9%) suggests that recommendations for adverse event management with symptomatic drugs and dose adjustment were successful and should be considered in clinical practice. Dose reduction for controlling adverse events did not impact the efficacy of nintedanib on reducing the rate of decline of FVC [48].

The INBUILD trial was designed based on the hypothesis that different types of fibrotic ILDs share common mechanisms. In this multicentric, RCT, were enrolled 663 patients with chronic fibrosing ILDs other than IPF who had > 10% extent of fibrosis on HRCT and met criteria for ILD progression in the prior 24 months. Overall, patients treated with nintedanib had a significantly slower FVC decline over 52 weeks than patients with placebo, with a between-group FVC difference of 104.0 ml in favor of nintedanib [41]. In the subgroup analysis of the 178 patients with autoimmune-ILD from INBUILD trial, including patients with progressive fibrotic SSc-ILD, the rate of decline in FVC was significantly reduced in the nintedanib-treated patients as compared to placebo (-75.9 ml/year versus -178.6 ml/year) over 52 weeks [49]. The effect of nintedanib was consistent across subgroups based on demographics, severity of ILD, or treatment use [50]. Based on these results nintedanib was approved for treatment of chronic fibrosing ILD with a progressive phenotype.

Pirfenidone, a pyridone derivative, has been tested in a small number of patients with SSc-ILD, with inconclusive results. In a small open-label phase II study (LOTUSS trial), pirfenidone was well tolerated, even when used in combination with MMF [51]. The efficacy of pirfenidone was not evaluated in this study. In the RELIEF study, a RCT on progressive fibrotic ILD that also included SSc-ILD patients, pirfenidone has been shown to significantly slow the disease progression, but the study was stopped due to slow recruitment [52]. The SLS III (Scleroderms Lung Study III), a phase-2, multicentric, double-blind study evaluated combination therapy MMF and pirfenidone versus MMF and placebo in SSc-ILD patients. In the combination therapy group a more rapid improvement of FVC% predicted was observed at 6 months, but there were no significant differences between groups at 18 months. The study was prematurely discontinued because it failed to recruit the intended number of patients [53]. Currently, pirfenidone is not licensed for SSc-ILD patients.

Autologous hematopoietic stem cell transplant

Refractory severe SSc is the main indication of autologous hematopoietic stem cell transplant (AHSCT) in autoimmune rheumatic disease. AHSCT involves the eradication of autoreactive T- and B-cells by high dose of immunosuppression, followed by reconstitution of the immune system by transplantation of autologous hematopoietic stem cells [54]. AHSCT is recommended by the 2017 European League against Rheumatism (EULAR) guideline in selected patients with rapidly progressive SSc at risk for organ failure, after careful assessment of the risk-benefit ratio [55].

Three RCTs demonstrated the benefits of AHSCT in improving skin fibrosis, lung function, quality of life and long-term survival in SSc patients [56–58].

The American Scleroderma Stem cell versus Immune Suppression Trial (ASSIST), a phase-2 monocentric RCT, enrolled 19 patients with SSc and organ involvement, and showed that AHSCT significantly improved skin and pulmonary function for up to 2 years in comparation to 6 months pulse therapy with CYC [56]. The Autologous Stem Cell Transplantation International Scleroderma (ASTIS) trial, a European multicentric phase-3 RCT, on 156 patients with early dcSSc (including 125 patients with ILD), compared AHSCT with CYC pulse therapy for 12 months. At 2 years follow-up, there were significant improvements with AHSCT versus CYC in FVC% predicted (6.3%mean vs - 2.8%; difference -9.1 [95% CI -14.7 to - 2.5], p=0.004) and total lung capacity (TLC%) predicted (5.1% vs -1.3%; difference -6.4 [95% CI -11.9 to - 0.9], p=0.02) [57]. In The Scleroderma: Cyclophosphamide or Transplantation (SCOT) trial, a phase-2 RCT conducted in multiple centers in the United States, 75 dcSSc patients with renal or pulmonary involvement (73 patients with ILD) were included. The study results did not show a significant difference in FVC% predicted between the AHSCT and CYC subgroups, but fewer patients developed respiratory failure in AHSCT group compared with patients treated with CYC. A recent metaanalysis of 3 RCT trials and a retrospective analysis showed a significantly better long-term survival and overall survival in AHSCT group in comparation with standard immunosuppressive treatment for severe SSc. It also confirmed the beneficial effect of ASHCT on skin thickness, lung function, and quality of life. Based on the results of these studies, AHSCT is considered an effective treatment option which can stabilize lung function in selected patients with dcSSc. However, further studies are needed to establish its role in the management of SSc-ILD [59].

Toxicity of AHSCT remains a major concern. AHSCT is associated with an increased risk of treatment-related mortality of approximately 5-10%. The early treatment-mortality was lower in the SCOT trial than in the ASTIS trial (2.6% versus 10%), probably due to differences between patient populations and transplant protocols, and due to differences in the centers expertise [60]. AHSCT is also associated with higher risk of viral infections, hematologic complications and cancers [56–58]. Considering the high risk of adverse events and early treatment-related mortality of AHSCT, the international guidelines recommend this treatment option for carefully selected SSc patients in highly experienced centers [55].

Lung transplantation

Lung transplantation is the only life-extended treatment option in SSc patients with end-stage lung fibrosis. The use of lung transplant is limited in SSc patients due to availability of donors and multimorbidity of these patients, that can have a negative impact on lung transplantation outcomes. Gastroesophageal reflux may cause obliterative bronchiolitis after transplant and is thought to be a risk factor for post-transplant allograph dysfunction. Recent cohort studies showed similar post-transplant outcomes in SSc-ILD compared to other causes of ILD [61,62]. In a recent retrospective multicentric observational study of 90 patients who received lung transplants, survival rates after 1, 3, and 5 years were 81%, 68%, and 61%, respectively. The main predictors of poorer survival were female gender and the presence of pulmonary arterial hypertension [63].

Treatment approaches in clinical practice

Treatment strategies in clinical practice are mainly based on expert opinion and consensus guidelines. The management of SSc-ILD requires a multidisciplinary approach and should be individualized based on factors such as SSc phenotype, disease duration, ILD severity, risk factors for progression, evidence of progression, comorbidities, and preference of patients. The treatment goal in SSc-ILD is stabilization of lung function or attenuation of disease progression. Not all patients should be treated specifically for SSc-ILD. The decision to initiate and change the treatment should be based on assessment of the current disease state and the disease progression (risk, extent, speed of progression) [32,64].

Experts recommend that immunosuppressive agents should be used in patients with subclinical SSc-ILD and high risk for progressive disease and in patients with clinical ILD in early phases of the disease. Current guidelines suggest MMF as first-line therapy for SSc-ILD. As second- and third-line agents, CYC, RTX and TCZ are recommended. The use of CYC is time-limited due to significant adverse events and is recommended in clinically significant ILD. Rituximab seems to be a good alternative to CYC with a better safety profile. TCZ is recommended in patients with early dcSSc, with progressive skin disease, elevated acute phase reactants and clinically significant ILD. Corticosteroids are not effective in SSc-ILD and are associated with high risk of adverse events. Nintedanib is considered a therapeutic option for patients with fibrotic ILD despite immunosuppressive therapy. Early introduction of antifibrotic agents may be beneficial in patients with SSc-ILD and high risk of progressive disease, but the risk-benefit ratio must be taken into consideration. Nintedanib is recommended as first-line monotherapy only in patients with fibrotic ILD without active skin or musculoskeletal involvement. Patients with clinically significant ILD and signs of extra-pulmonary active disease may benefit from combination therapy with MMF and nintedanib as first-line treatment. In patients with refractory and progressive SSc-ILD escalation therapy may include AHSCT, lung transplant or clinical trials [32,45,55,65].

Conclusions

ILD is a frequent complication of SSc and is

associated with high morbidity and mortality. Screening for SSc-ILD is essential for early detection and optimization of disease management in all patients. Patients should be closely monitored for ILD progression with regular PFTs and assessment of symptoms, and with follow-up HRCT scans, when required. Early identification and timely treatment in patients with progressive ILD may improve the outcome. Recent advances have expanded treatment options for SSc-ILD, which currently include immunosuppressive and antifibrotic agents. Patient stratification is needed to optimize treatment outcomes in terms of benefits and risks. Effective management of SSc-ILD remains a challenge in clinical practice, due to high heterogeneity in clinical presentation, disease course and responsiveness to treatment. Further large randomized controlled and prospective studies are needed to provide more evidence for the efficacy and safety of these drugs and to establish the optimal treatment strategy of SSc-ILD.

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