SCLERODERMA-ASSOCIATED INTERSTITIAL LUNG DISEASE – NEW THERAPEUTIC APPROACH

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Abstract. Scleroderma is a systematic autoimmune disease characterized by endothelial dysfunction which causes small vessel disease, fibroblastic disorder with excessive production of collagen and fibrosis, as well as immunological disorders. Direct lung damage leading to interstitial lung disease is developed early after diagnosis. The result is a rapid decline in pulmonary function with worsening of quality of life and severe disability in these patients. The purpose of this review is to present all known medicaments for treatment of patients with scleroderma-associated interstitial lung disease – not only approved, but also those still being researched. Modern tendencies require the therapy to be guided by both rheumatologists and pulmonologists, as well as the participation of highly qualified radiologists. Correct clinical approach will enable the achievement of maximum results aimed at improving the quality of life and its duration in this group of patients.

Key words: Scleroderma-associated interstitial lung disease, immunosuppressant drugs, biological therapy, antifibrotic drugs

Scleroderma is a systematic autoimmune disease characterized by endothelial dysfunction which causes small vessel disease, fibroblastic disorder with excessive production of collagen and fibrosis, as well as immunological disorders. The overall incidence rate of scleroderma worldwide is about one in 10,000 individuals [1]. The frequency and prevalence rates for Europe, the USA, Australia and Argentina are quite similar – 150-300 cases per million, with Scandinavia, Japan, the United Kingdom, Taiwan and India having a slightly lower prevalence [2]. The female to male ratio is 4:1, with the main age group developing the disease being 45-55 years [3].

Depending on the localization of the skin changes, two forms of the disease are distinguished: systemic scleroderma and localized scleroderma [4]. In the course of the disease, all organs and systems can be affected, but lung involvement is one of the crucial ones. The lungs can be affected by scleroderma due to:

- Direct lung injury;
 - Indirect pulmonary complications;
 - Combination of direct and indirect damage;
 - Other lung diseases not related to scleroderma
- COPD/emphysema, asthma, lung nodules, etc.

There are two main types of direct lung injury – interstitial lung disease (ILD) and pulmonary hypertension (PH). The two forms, ILD and PH, together account for about 60% of scleroderma-related mortality [5]. In an Italian cohort the survival of patients with scleroderma-associated ILD after 10 years was

reported to be about 29-69% with a female/male ratio of 9.7: 1 [6]. In the African American race, scleroderma has an earlier clinical onset, with more severe lung involvement. East Asians have the longest survival period (43.3 years) and Arabs – the shortest (15 years) [7]. Early diagnosis and timely treatment of pulmonary complications are very important for the survival of these patients. ILD and PH are found in all forms and phases of the disease. However, while ILD is more common in the systemic form, PH is more common in the localized form. Sometimes ILD can occur in scleroderma without any skin changes, the so-called scleroderma sine scleroderma [8].

Pulmonary parenchyma involvement develops early after the diagnosis of scleroderma. Approximately 25% of patients develop clinically significant lung disease within 3 years after the detection of physical and X-ray changes or abnormalities in bronchoalveolar lavage (BAL) [9]. Risk factors for this include African American race, skin score, serum creatinine and creatinine phosphokinase, hypothyroidism, cardiac involvement, and genetic factors [7, 10].

CELLULAR COMPOSITION OF BAL

Deviations in the normal cellular composition of BAL (neutrophils $\geq 3\%$ or eosinophils $\geq 2\%$ in BAL) occur in 38-72% of patients with scleroderma and parenchymal involvement shown by high-resolution computed tomography (HRCT) [11]. 50% of patients

with normal HRCT also showed abnormalities in the cellular composition of BAL. In some cases, lymphocytes and mast cells may be elevated [7]. In an analysis of BAL in 156 patients with scleroderma-associated ILD it was found that the high percentage of neutrophils in BAL is associated with a 30% increased risk of death [12]. However, this cellular test is not used as a prognostic sign for the evolution of the disease, but rather serves to exclude infections as well as for scientific purposes [13]. In scleroderma-associated ILD an increase in the pro-inflammatory cytokines interleukin (IL) -8, tumor necrosis factor- α (TNF) - α and macrophage inflammatory protein-1 α in BAL has been found [14]. Elevated IL-33 levels are associated with the severity of the fibrotic changes in the skin and lungs [15].

PATHOANATOMICAL CHANGES

It is suggested that myofibroblast differentiation and proliferation are a key pathological mechanism for the development of pulmonary fibrosis in patients with scleroderma [7]. The main histological finding is nonspecific interstitial pneumonia (NSIP), while the second most common one is usual interstitial pneumonia (UIP) [16]. When comparing the lung biopsy of patients with idiopathic pulmonary fibrosis versus scleroderma-associated ILD, more germinal centers and fewer fibroblast foci were found in patients with scleroderma [1, 7]. Lung biopsy in patients with scleroderma-associated ILD demonstrated an increased expression of Toll-like receptor (TLR) 4 in fibroblasts [7, 17]. TLR4 is widely recognized as central to the innate immune response against gram-negative bacteria, but can also be activated by a variety of endogenous factors produced as a result of cellular injury, autoimmune response, or oxidative stress. Its role in the activation of fibrogenesis has been proven [7].

The clinical picture of scleroderma-associated ILD most often includes symptoms of shortness of breath, fatigue and nonproductive cough, but early ILD is often asymptomatic. Auscultation reveals bilateral fine inspiratory crackles at the lung bases [7].

DIAGNOSTIC TESTS

Serological tests – anti-topoisomerase and anti-endothelial cell antibodies, are predictors of lung damage, while anti-centromere and anti-RNA polymerase III antibodies are less associated with pulmonary involvement [18]. Predictors of severe restrictive lung disease ($FVC \leq 50\%$ of predicted) are African American race, male gender, the degree of

physiological disturbances at diagnosis (forced vital capacity – FVC, and diffusing capacity for carbon monoxide – DLCO), the younger age [7].

The „gold“ standard for non-invasive diagnosis of scleroderma-associated ILD is HRCT. The examination reveals changes such as „ground glass opacities“ and/or „honeycomb“, reticular fibrosis. Reversibility of the changes is rarely possible. About 2/3 of patients with ground glass opacities develop fibrosis regardless of their therapy [19]. In some cases of patients with abnormalities in pulmonary function tests and physical examination (crackles) HRCT may be normal, with changes appearing at a later stage. Normal HRCT predicts a low probability of developing scleroderma-associated ILD (85% of these patients remain with a normal HRCT image at a mean follow-up of 5 years) [7].

PULMONARY FUNCTION TESTS

A decrease in FVC is found in 40-75% of patients, about 15% of whom have a severe reduction. DLCO is reduced in almost all patients with other changes in pulmonary function tests, correlating with the degree of pulmonary involvement shown by HRCT. DLCO levels (adjusted to hemoglobin) were lower in patients with histopathological patterns of common interstitial pneumonia. FVC and DLCO are markers of pulmonary involvement, but the decrease in DLCO by itself is a more significant marker of poor outcome [20].

Depending on the changes detected from HRCT, as well as the FVC values, scleroderma-associated ILD is classified as extensive ($HRCT > 20\%$; $FVC < 70\%$) or limited ($HRCT < 20\%$; $FVC > 70\%$) lung involvement. It has been found that patients with more extensive involvement have a higher mortality rate than those with limited [7, 21].

TREATMENT

Treatment of scleroderma-associated ILD includes immunosuppressive drugs. Despite that, optimal therapy has not yet been established. Clinical trials of various drugs are ongoing with the aim being to stop stopping the progression of the disease rather than regression of the changes. Currently, several immunosuppressant drugs are being used. After starting treatment with them, the changes in pulmonary function tests (the decrease) as well as the X-ray changes are strictly monitored. Improvement from the immunosuppressive therapy is more likely to occur in the early stages of the disease rather than when loss of lung function occurs. The

quickest decline in FVC values is reported in the first three years after the onset of the disease. After initiation of treatment, physical tolerance and pulmonary function tests should be monitored every six months, with frequent HRCTs not being recommended and having sense of being conducted in the event of a change in the symptoms. Most doctors prefer to treat patients with extensive pulmonary involvement (according to HRCT and lung biopsy results) with a pattern of usual interstitial pneumonia with ground glass opacities involving more than 10% of the lungs. The results of various new randomized clinical trials, which may or may not include immunosuppressive agents and other drugs that demonstrate efficacy in the treatment of scleroderma-associated ILD, are constantly being published [7, 22, 23].

Cyclophosphamide (CYC), mycophenolate mofetil (MMF) or rituximab (RTX) are used as an induction therapy for treatment of scleroderma-associated ILD. Maintenance therapy follows, but there is no consensus on the most appropriate drugs and regimens for their application, as well as how well patients respond to particular therapy [24, 25].

– Cyclophosphamide (CYC)

The effect of orally applied cyclophosphamide (CYC) was reported in the Scleroderma Lung Study 1, in which it was compared with placebo. At the month 12 from the start of treatment a difference in FVC of 2.53% in the CYC group, compared to the placebo group was found ($p < 0.03$). An improvement in dyspnea, the quality of life, the skin changes and physical capacity has also been reported. An improvement in Total Lung Capacity (%) (TLC), but not in DLCO (%) was found as well. The 24-month follow-up showed persistence in the difference between both groups only in terms of dyspnea, but not in the other indicators. Monthly intravenous administration of CYC is preferred over oral due to the lower cumulative dose, less frequently observed side effects, and the ability to provide adequate hydration prior to administration. The most commonly observed side effects are infertility, opportunistic infections, hemorrhagic cystitis, bladder cancer and neutropenia. Six-month intravenous infusions are recommended, with monthly monitoring of white blood cell count, renal function and urine. Combinations of corticosteroid pulses and CYC with favorable results were used. After completing a course of CYC, the maintenance treatment is usually continued with the less toxic MMF or Azathioprine. Improvement in lung function after CYC treatment tends to decrease after its discontinuation [25-28].

– Mycophenolate mofetil (MMF)

Mycophenolate mofetil (MMF) is an inhibitor of lymphocyte proliferation, commonly used in patients with ILD who are at risk of disease progression. The reasons for its use are based mainly on the results of the "Scleroderma Lung Study II". It includes 142 patients with scleroderma-associated ILD having FVC $< 80\%$ and ground glass opacities by HRCT. Participants received either 1500 mg MMF twice daily for 24 months or oral CYC titrated to a maximum dose of 1.8-2.3 mg/kg for 12 months. The results show higher tolerance towards MMF than to CYC, with a lower incidence of leukopenia and thrombocytopenia. The most common adverse effects reported during MMF therapy are bone marrow suppression and gastrointestinal symptoms. To prevent these adverse effects, complete blood count monitoring is required at the beginning of the therapy and periodically during treatment. To avoid gastrointestinal complaints, the daily dose of MMF (usually between 1.5 and 3 g per day) is divided into two doses. The study demonstrates that MMF is just as effective as CYC and has similar adverse effects over a 24-month treatment period [29].

When comparing MMF to placebo, there was an improvement in FVC (%) ($p < 0.0001$), DLCO % ($p < 0.001$) and dyspnea ($p = 0.0112$) [30].

Stratton et al. conducted an observational study in which 13 patients received anti-thymocyte globulin plus prednisolone for 5 days, followed by maintenance MMF therapy for 12 months. Long-term MMF therapy is well tolerated, but no change in mean FVC or DLCO has been reported after receiving this combination therapy [31]. Other studies involving MMF are ongoing, the results of them are being awaited [32].

– Azathioprine(AZA)

Azathioprine is less effective than CYC for the initial treatment of scleroderma-associated ILD. In a randomized double-blind study, 60 patients with early scleroderma-associated ILD received AZA or CYC. During the first 6 months of the trial, the patients also received prednisolone. After 18 months, FVC ($-11.1 \pm 1\%$) and DLCO ($-11.6 \pm 1.3\%$) were significantly worse ($p < 0.001$) in the AZA group, while in the CYC group they remained unchanged [33]. In another study, an initial prednisolone therapy in combination with venous CYC was followed by a maintenance therapy with AZA or placebo. Although a slight improvement in FVC was observed in the AZA group compared to placebo, the difference was not statistically significant [34].

– Corticosteroids (CS)

The initial therapy does not include corticosteroids due to the risk of scleroderma renal crises, especially in patients with systemic scleroderma. In an observational study involving 3778 patients with scleroderma-associated ILD, glucocorticoids were used in more than half of the patients, but even at doses > 20 mg/day, the positive effect on lung function was mild and presented only in patients with FVC > 75% [35]. A study by Tochimoto et al. reported an effect in some patients with scleroderma in terms of interstitial pulmonary changes during pulse therapy with intravenous CYC and prednisolone [36].

– Cyclosporine and Tacrolimus

Cyclosporine and tacrolimus selectively inhibit calcineurin, thereby disrupting the transcription of IL-2 and other cytokines in T-lymphocytes. Cyclosporine is an immunosuppressive agent that is used mainly after organ transplantation to prevent graft rejection. It is highly nephrotoxic, leading to a decrease in glomerular filtration rate (GFR) and creatinine clearance [7]. In a retrospective study by Ichimura et al. twenty patients with scleroderma-associated ILD initially treated with CYC were divided into two groups. Subsequent therapy after CYC in the first group was a combination of tacrolimus and low doses of CS, and in the second group – only low doses of CS. No statistical difference was observed in the baseline pulmonary function tests for both groups (% VC: $79.5 \pm 16.1\%$ vs. $87.4 \pm 18.8\%$, % DLCO: $59.5 \pm 11.5\%$ vs. $63.7 \pm 14.6\%$). After a 3-year follow-up, patients treated with tacrolimus showed no signs of disease progression [37]. However, neither cyclosporine, nor tacrolimus are included in the standard recommendations for treatment of scleroderma-associated ILD [7].

– Bosentan

Bosentan is a non-selective endothelin receptor antagonist used in the treatment of pulmonary hypertension. The idea for its use in scleroderma-associated ILD is the involvement of the endothelin system in the pathogenesis of scleroderma. The assumptions are that it may slow down the progression of the lung changes. In this regard, a prospective, double-blind, randomized, placebo-controlled, parallel group study was conducted. In it Seibold et al. assess the changes in 6-minute walking distance and the worsening of pulmonary function tests. Of the 163 patients, 77 were randomized to receive Bosentan and 86 received placebo over a period of 12 months. At the end of the study, there was no significant difference between the groups in terms

of the distance reported from the 6-minute walking test. FVC and DLCO remained stable and no deaths were reported during the study period. In conclusion, the study data did not report benefits from the use of endothelin receptor antagonists in the treatment of scleroderma-associated ILD [38].

– Biological therapy

Rituximab (RTX)

RTX is a monoclonal antibody targeting CD20-positive B-lymphocytes, which is recommended for the treatment of patients with refractory scleroderma-associated ILD [39]. In a pilot study by Daoussis et al. RTX plus standard therapy (prednisone, CYC and/or MMF) was compared to standard therapy alone. The results showed that the eight patients in the RTX group had significantly better FVC and DLCO after one year compared to the other six patients who received only standard therapy (mean improvement rate of 10.25% versus 5.04% for FVC, $p = 0.002$ and 19.46% vs. 7.5% for DLCO, $p = 0.023$, respectively) [40]. Giuggioli et al. reported the results of a study in 10 patients with scleroderma treated with RTX, while their ongoing treatment was left unchanged. Patients have had a mean age of 46 ± 13.5 years with average disease duration of 6.3 ± 2.7 years. They were treated with one or more RTX cycles (4 weekly infusions of 375 mg/m²). The main indications for RTX therapy were interstitial pulmonary fibrosis (in eight patients), cutaneous, and/or articular manifestations unresponsive to previous therapies. The effects of RTX have been assessed after 6 months of the first cycle as well as at the end of the long-term follow-up period (37 ± 21 months, range 18-72 months). The results of the study showed improvement in cutaneous and articular manifestations after RTX administration, stabilization of fibrotic changes in 6 of the patients and worsening in two [41]. In a series of four patients with scleroderma-associated ILD, Mohammed et al. reported pulmonary fibrosis improvement in one patient and retention of fibrotic changes in two, demonstrated by HRCT. In the meantime, they reported a preventive effect of RTX on FVC decline [42]. In a significantly larger number of patients – 51, Melissaropoulos et al. have reported a positive effect after long-term administration of RTX in regard to lung function and skin fibrosis in patients with scleroderma [43]. Other studies have also reported a positive effect after RTX administration in patients with scleroderma-associated ILD [44-46]. The results of the RECOVER study (NCT01748084) are expected. One of its secondary endpoints is to determine the

role of RTX on lung function. The RECITAL study (NCT01862926), in which patients with various connective tissue diseases, incl. scleroderma, were randomized, is underway. The aim of this study is to compare the change in FVC when administering intravenous RTX versus intravenous CYC [25, 32].

Tocilizumab

Tocilizumab is a humanized monoclonal antibody directed against the human IL-6 receptor. It is approved for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis and Castleman disease [47]. In patients with mild scleroderma-associated ILD, higher serum IL-6 levels seem to predict early disease progression, which may serve as an indicator for treatment adjustment [48]. 87 patients with systemic scleroderma were included in a randomized, double-blind, placebo-controlled study (Khanna et al.). At week 24 a significantly lower decrease in FVC in the Tocilizumab group compared to placebo was reported (−34 versus −171 ml, respectively, $p = 0.0368$). However, at week 48, no significant difference in FVC was found between the treated and placebo groups ($p = 0.0990$). At week 24, worsening of the predicted % FVC was observed in fewer patients on Tocilizumab therapy than on placebo ($p = 0.009$). This relation remains the same at week 48 ($p = 0.0373$). At week 24, 3% of patients treated with Tocilizumab and 19% of those treated with placebo had a reduction in predicted FVC > 10%. At week 48, a decrease of more than ten percent was seen in 10% of patients on active therapy compared to 23% of those on placebo [49].

Belimumab

Belimumab is a recombinant human monoclonal anti-BLyS antibody that has been approved by the US Food and Drug Administration (FDA) for the treatment of systemic lupus erythematosus. The first clinical trial examining the effect of Belimumab in patients with scleroderma had a very small number of participants. In it 9 patients were on therapy with Belimumab + MMF, and another nine – on a combination of placebo + MMF. At week 52, the reported mean changes in the predicted FVC % were 5.00 (0.00, 8.00) versus −2.00 (−6.00, 4.00), and the changes in the predicted DLCO % 2.00 (−7.00, 7.00) versus 0.00 (−6.00, 7.00), respectively [50].

Pomalidomide (POM)

Pomalidomide (POM) is an immunomodulator with antiangiogenic properties and cytotoxic activity. It is approved for the treatment of relapsed or refractory multiple myeloma [51]. The results of a 52-week randomized, double-blind clinical trial (Hsu et al.)

in 23 patients with scleroderma-associated ILD on POM or placebo therapy showed worsening of FVC in both groups (POM −5.2%, placebo −2.7%). The study was discontinued due to lack of efficacy [52].

Bortezomib

Bortezomib is an FDA approved drug for the treatment of multiple myeloma. It inhibits TGF-signals in vitro, supporting normal recovery and preventing pulmonary fibrosis. The aim of a 24-week clinical study is to evaluate whether bortezomib, MMF or the combination of both present superiority at treating scarring of the lung caused by scleroderma. Participants were randomized to receive MMF (1.5 g twice daily orally) and Bortezomib (1.3 mg/m²) subcutaneously once weekly for the first 2 weeks or MMF plus placebo (normal saline) for 24 weeks. The results of the study are being awaited [53].

Abituzumab

Abituzumab is a humanized αv integrin-targeted monoclonal antibody with potential antifibrotic effects. The aim of one study (Khanna et al.) is to compare two doses of abituzumab (500 mg or 1500 mg given intravenously every four weeks) with placebo and to determine if abituzumab is more effective, safer, more tolerable and whether it can provoke a better immune response than placebo in the treatment of patients with scleroderma-associated ILD who are already receiving constant doses of MMF. The primary endpoint is to report the change in FVC at week 52. The results of the study are being expected [54].

SAR156597

SAR156597 is a bispecific monoclonal antibody directed against IL-4 and IL-13. The clinical trial NCT02921971, which aims to clarify its role in the treatment of patients with scleroderma, is underway [32, 55].

– Dabigatran

Dabigatran is a direct thrombin inhibitor that could theoretically improve pulmonary fibrosis. Because of this a study was conducted to assess its tolerability and adverse effects in the treatment of patients with scleroderma-associated ILD. The results are encouraging, but due to the small number of participants (13 patients) larger randomized trials are needed [56].

– Antifibrotic drugs

Pirfenidone

Pirfenidone is an antifibrotic drug approved for use in patients with idiopathic pulmonary fibrosis (IPF). Miura et al. reported the effect of pirfenidone

(1200-1800 mg/day) in five patients with scleroderma-associated ILD. Its use is associated with a decrease in dyspnea and an increase in VC (10%) from the baseline [57]. A 16-week open-label phase II study of the safety and tolerability of pirfenidone in patients with scleroderma-associated ILD showed that pirfenidone was generally well tolerated, but no significant changes in FVC were reported [58]. SLS III (Scleroderma Lung Study III; NCT03221257) is a double-blind, parallel-group, placebo-controlled, randomized phase II study aimed at determining the efficacy and safety of the combination of MMF with pirfenidone in the treatment of patients with symptomatic scleroderma-associated ILD. The study is ongoing and the results are being awaited [32]. Another clinical trial (NCT03856853), which is also currently ongoing, aims at evaluating the efficacy and safety of pirfenidone in patients with scleroderma-associated ILD. The main indicator to be monitored is the relative change from baseline in FVC% over a period of 52 weeks [32]. Isolated clinical cases in which patients treated with pirfenidone had an improvement in pulmonary function have been reported [59, 60]. Good effects from the combination of pirfenidone and CYC for the treatment of scleroderma-associated ILD have also been reported, but larger studies are still needed [61].

Nintedanib

Nintedanib is a small-molecule tyrosine kinase inhibitor that targets vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF) and colony stimulating factor 1 (CSF1R) receptors. The drug slows down the progression and improves survival in patients with idiopathic pulmonary fibrosis, and has already been approved by the FDA and European Medicines Agency (EMA) for the treatment of scleroderma-associated ILD as well [7]. In the INBUILD study the annual decrease in FVC, calculated on the basis of its change over 52 weeks in patients with interstitial lung changes as a result of various diseases, was estimated. The change in FVC in the nintedanib group was -80.8 ml per year and in the placebo group was -187.8 ml, with an intergroup difference of 107.0 ml per year (95% confidence interval [CI], 65.4 to 148.5; $p < 0.001$) [62]. The efficacy and safety of oral nintedanib (150 mg) for the treatment of scleroderma-associated ILD were evaluated in the SENCIS study. It was a double-blind, placebo-controlled and randomized study in which patients were treated for at least 52 weeks with nintedanib. 50% of the study participants had disseminated skin involvement from scleroderma and were on therapy

with stable doses of MMF. One of the study inclusion criteria is the presence of fibrosis affecting at least 10% of the lungs shown by HRCT. The primary endpoint is to estimate the annual rate of FVC decline. The main secondary endpoints are assessments of the skin changes and the overall result of the Saint George respiratory Questionnaire (SGRQ). Neither of the two secondary endpoints showed a statistical difference between both arms at the end of the study. The corrected annual change in FVC was -52.4 ml per year in the nintedanib group compared to -93.3 ml per year in the placebo group. Nintedanib slows down the decrease in FVC by 44% in a 52-weeks treatment period (difference of 41.0 ml per year compared to placebo; 95% [CI], 2.9-79.0; $p = 0.04$). In patients on therapy with stable doses of MMF, no further improvement was observed with the addition of nintedanib. The main adverse effect reported in the study was diarrhea. It has been reported in 75.7% of patients treated with nintedanib versus 31.6% of patients on placebo [63]. 450 patients continued their participation in a follow-up open-label, uncontrolled study with the aim of evaluating the long-term safety of nintedanib therapy (SENSCIS-ON study). It is expected to end in July 2021 [7].

Other tyrosinekinase inhibitors

Imatinib is not shown to have apparent efficacy in treatment of scleroderma-associated ILD and is generally not well tolerated. In open-label clinical trials, therapy with Nilotinib and Dasatinib did not show significant clinical efficacy [7, 25].

– Autologous hematopoietic stem cell transplantation (AHSCT)

AHSCT is offered as a potential therapy in patients with severe scleroderma. In a meta-analysis involving patients with scleroderma-associated ILD on CYC therapy, AHSCT reduced overall mortality (risk ratio [RR], 0.5 [95% CI, 0.33-0.75]) and improved FVC (mean difference 9.58 (95% CI, 3.89-15.18)), total lung capacity (6.36% [95% CI, 1.23-11.49]), and the quality of life (6.99% [95% CI, 2.79-11.18]) [7, 64]. Therapy-related mortality varies between studies, but is generally higher in AHSCT (RR, 9.00 [95% CI, 1.57-51.69]) [7]. In the ASSIST study (Autologous Stem Cell Systemic Sclerosis ImmuneSuppression), hematopoietic stem cell transplantation and anti-thymocyte globulin therapy preceded by treatment with CYC and filgrastim were superior to CYC in terms of skin changes and lung volumes, although no difference in DLCO was found. No deaths were reported in any of the groups during the 24-month follow-up

period [65]. The aim of the SCOT study (Scleroderma: CYC or transplantation) has been to evaluate the efficacy and safety of high-dose immunosuppressant therapy after AHSCT versus CYC therapy in patients with severe scleroderma with extensive skin involvement and lung or kidney involvement. Myeloablative CD34 + AHSCT results in a longer survival period without adverse events (significant organ damage or death) compared to 12 months of CYC. Better survival was reported at 54 months (79% vs. 50%; $p = 0.002$) and at 72 months (74% vs. 47%; $p = 0.03$) [7, 66].

– Lung transplantation

Lung transplantation should be considered early in the event of respiratory failure in all patients with chronic lung diseases. Unfortunately, gastrointestinal comorbidities, common in patients with scleroderma-associated ILD, may compromise the assessment of transplantation [7]. Khan et al. compare survival after lung transplantation in patients with scleroderma to those with other diseases [67]. Survival after transplantation in patients with scleroderma varies from 69-91% in the first 30 days after surgery to 46-79% after three years. The short- and medium-term survival in patients with scleroderma is similar to those who have undergone surgery for another reason [7, 67].

CONCLUSION

Scleroderma-associated ILD has an incompletely clarified pathogenesis, a difficult-to-predict clinical course, and relatively ineffective therapeutic approaches. Despite the many drugs used to treat patients with scleroderma-associated ILD, there are still many open questions. The choice of when and how to start therapy, how long the treatment should be, and others require the establishment of a universal consensus for treatment. Well-established drugs such as MMF and CYC are used alongside new anti-fibrotic drugs or biological agents. In refractory cases, AHSCT and lung transplantation are considered. More randomized trials are needed to elucidate the role, location, efficacy, and safety of the various treatment regimens. In all cases, however, therapy should be performed together by rheumatologists and pulmonologists in order to achieve the best results to improve the quality of life and its duration in these patients.

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