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REVIEW
DERLEME

Current treatment of systemic sclerosis-associated interstitial lung disease

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ABSTRACT

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Systemic sclerosis (SSc) is a connective tissue disease characterized by immune irregularity, vasculopathy and excessive collagen production, which causes skin and internal organ fibrosis. Although SSc often affects multiple organs and/or systems, lung involvement and especially interstitial lung disease (ILD) are the leading cause of death in this disease. The fact that different treatment options have been raised in recent years has given hope to clinicians in the management of this disease. This article will also review the current treatment options of SSc-ILD.

Key words: *Systemic sclerosis; interstitial lung disease; treatment*

ÖZ

Sistemik sklerozis ilişkili interstisyel akciğer hastalığının güncel tedavisi

Sistemik skleroz (SSc), deri ve iç organ fibrozisine neden olan ve vaskülopati, immün sistem işlev bozukluğu ile giden bir bağ dokusu hastalığıdır. Sistemik skleroz, sıklıkla birden fazla organı ve/veya sistemi etkilese de akciğer tutulumu ve özellikle de interstisyel akciğer hastalığı (İAH) bu hastalıkta önde gelen ölüm nedenidir. Son yıllarda farklı tedavi seçeneklerinin olması bu hastalığın yönetiminde klinisyenlere umut vermiştir. Bu makalede SSc-İAH'nin güncel tedavi seçenekleri gözden geçirilecektir.

Anahtar kelimeler: *Sistemik sklerozis; interstisyel akciğer hastalığı; tedavi*

INTRODUCTION

Systemic sclerosis (SSc) is an autoimmune disease of unknown cause that leads to fibrosis in the skin and internal organs. The most frequently observed event is skin involvement in this dis-

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ease. Lungs, digestive system and the heart are also commonly affected by the disease (1). Systemic sclerosis associated lung disease is frequently presented as interstitial lung disease (ILD) or pulmonary arterial hypertension (2). Lung involvement is the leading cause of mortality in SSc. While clinically significant lung involvement is observed in approximately 50% of the patients, it has been reported that lung involvement occurs at a rate of 90% according to autopsy findings (3).

Pathogenesis

Two theories have been emphasized regarding the pathogenesis of systemic sclerosis-associated ILD: immune-mediated inflammation and vasculopathy. These two factors probably induce pulmonary fibrosis together (4-8). In SSc-ILD, pulmonary fibrosis is characterized by activation of fibroblasts and extracellular matrix accumulation, and pathological samples show signs of vascular obliteration, fibrosis and inflammation (3). Microvascular damage, another characteristic feature of the disease, is considered to activate the coagulation pathway and lead to prothrombin secretion (9), which stimulates the endothelial cells and myofibroblast differentiation and increases transforming growth factor-β (TGF-β) production. Transforming growth factor-β is also released from activated lymphocytes and monocytes and plays a significant role in the development of fibrosis by stimulating the synthesis of extracellular matrix. Microvascular endothelial cell damage also increases endothelin-1 (ET-1) expression. Endothelin-1 which is known to be a potent vasoconstrictor peptide also contributes to the development of fibrosis. Endothelin-1 increases ESM production of fibroblasts, and from this aspect, it has a profibrotic effect similar to that of TGF-β. In conclusion, collagen accumulation in the tissues occurs as a result of the associations between endothelial cells, mononuclear cells and fibroblasts.

Clinical Findings

Patients with SSc-ILD may be asymptomatic in the early stage of the disease. However, the most common symptoms observed in symptomatic patients at an early stage include exertional dyspnea, dry cough and fatigue. Fine inspiratory crackles are often heard at the bases of both lungs during physical examination. Cyanosis due to hypoxia may be seen in patients with advanced disease.

Radiological Findings

Imaging is of great importance for the diagnosis of SSc-ILD and detection of the extent and severity of the disease. Although signs of increased interstitial scarring may be observed on chest radiographs used in lung imaging, it is also known that this method is not sensitive enough to detect ILD at an early stage. The gold standard imaging method for diagnosing ILD is high-resolution computed tomography (HRCT) (15). The most common radiological pattern observed in SSc-ILD is non-specific interstitial pneumonia (NSIP) followed by usual interstitial pneumonia (UIP) (16). While HRCT findings of NSIP include thickening in interlobular septa, ground-glass appearance, increase in reticular scarring (Figure 1), findings of UIP pattern include traction bronchiectasis, subpleural cysts and honeycomb formation (Figure 2) (17).

Pulmonary Function Testing

The results of pulmonary function testing (PFT) may be normal in the early stage of SSc-ILD. Decrease in isolated diffusing capacity of the lungs for carbon monoxide (DLCO) is one of the abnormalities that may be observed at an early stage. In the PFT of patients with significant SSc-ILD, a restrictive pattern characterized by decreased forced vital capacity (FVC), total lung volume and diffusing capacity of the lungs for carbon monoxide (DLCO) is frequently observed. Forced expiratory volume per second (FEV_1)/FVC ratio is usually found to be increased or normal. It has been demonstrated that the extent of

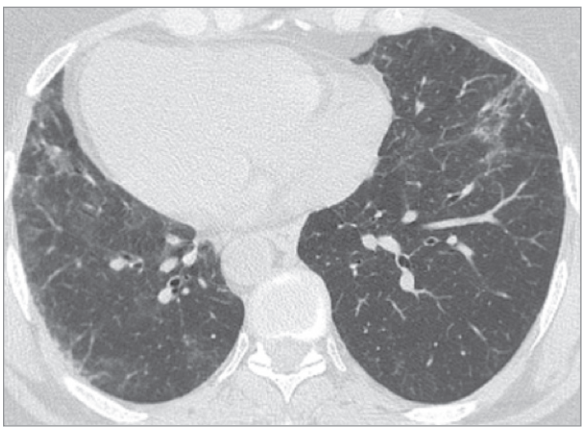


Figure 1. Areas with ground-glass appearance (non-specific interstitial pneumonia-NSIP) where the subpleural area is preserved in the lower lobes of both lungs in thorax CT.

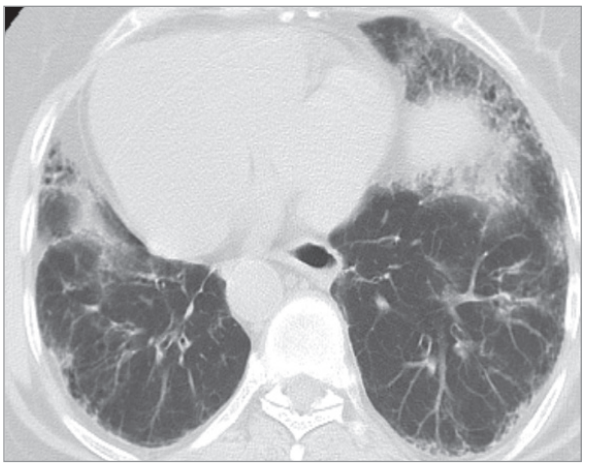


Figure 2. Diffused, subpleural non-specific alveolar-interstitial density increased in the basal segments of both lower lobes of the lungs, pleural roof distorted, sequentially large and small cystic lesions (honeycomb) present (usual interstitial pneumonia-UIP) in HRCT.

HRCT findings and decrease in FVC are two of the most important parameters in the detection of lung involvement severity (18).

Bronchoalveolar Lavage and Lung Biopsy

Bronchoalveolar lavage (BAL) is not a compulsory procedure for the diagnosis of ILD in SSc patients. However, BAL may be performed for the differential diagnosis of a suspected drug-related lung disease, infection or malignancy. It has been known that the number of granulocytes (particularly neutrophils and eosinophils) are increased in BAL samples of the patients with SSc-ILD (19). Routine lung biopsy is not necessary to be performed for ILD diagnosis in SSc patients. However, it may be performed if the diagnosis or malignancy is suspected.

Treatment of SSc-ILD

To date, many agents have been tried in the treatment of SSc-ILD and no results that would positively affect the course of disease could be obtained with most of these agents. Administration of a low-dose glucocorticoid in combination with an additional immunosuppressive agent lays the foundation of SSc-ILD treatment.

Cyclophosphamide

Cyclophosphamide (Cyc) is one of the oldest and most studied agents in the treatment of SSc. Positive effects of Cyc have been demonstrated both in uncontrolled, retrospective and observational studies and randomized, controlled studies (20-27). In their prospective, randomized, controlled trial, Tashkin et al. have reported that Cyc treatment administered orally for 12 months exhibited a moderately positive effect on respiratory functions and dyspnea score compared to placebo (2.53% improvement in FVC value) and that this effect was preserved up to 24 months after the discontinuation of treatment (27,28). Cyclophosphamide is administered via intravenous infusion (montly dose of 15mg/kg) or oral (daily dose of 2mg/kg) and given in combination with a low-dose glucocorticoid (prednisolone <10 mg/day or another equivalent glucocorticoid) in both treatment regimens (26).

Mycophenolate Mofetil

Mycophenolate mofetil (MMF) is a drug that has anti-inflammatory and antiproliferative properties and inhibits lymphocyte proliferation. In small-scale retrospective and observational studies performed in SSc-ILD, it has been reported that MMF stabilized respiratory functions or had a positive effect on these functions (29-33). In the light of these data, Tashkin et al. have compared Cyc and MMF treatment for the first time in a randomized controlled study with Scleroderma Lung Study (SLS) II (34). It has been specified in this study that MMF was better tolerated and less toxic but had a similar efficacy with Cyc. It can be said based on currently available data that MMF is a good alternative treatment option for patients who cannot or do not want to use Cyc or experienced a lack of efficacy with Cyc.

Azathioprine

Azathioprine is a purine antimetabolite. They inhibit the synthesis of new purine nucleotides in various immune system cells, especially CD4 type T cells and prevent their proliferation (35). In a randomized controlled study comparing the efficacy of Cyc and azathioprine as a first-line treatment, it has been demonstrated that there was a significant worsening in both FVC and DLCO values in the azathioprine group. Therefore, azathioprine is generally used as a maintenance treatment after cyclophosphamide instead of an initial therapy in patients with SSc-ILD (36).

Rituximab

Rituximab (RTX) is a monoclonal antibody that depletes CD20-positive B cells. B cell-depleting treatments have been brought to the agenda and started to be used after obtaining evidence indicating that B

cell could play a role in the etiopathogenesis in SSc-ILD patients. There are reports suggesting that RTX is effective in patients with SSc-ILD in both open-label and randomized controlled trials and case reports (37-39). Despite these favorable data, there is a need for new large-scale, randomized controlled studies to demonstrate the efficacy of RTX treatment in SSc-ILD.

Tocilizumab

Due to high serum IL-6 levels in patients with SSc especially in those with extensive skin involvement and increased mortality among patients with very high IL-6 levels, treatments targeting this cytokine have been brought to the current agenda (40).

In a phase 2, randomized controlled faSScinate study evaluating the efficacy and safety of subcutaneous tocilizumab (TCZ) in SSc, it has been demonstrated that patients in the TCZ group had less reduction in FVC values compared to those in the control group in weeks 24 and 48 (41). In a randomized, double-blind, phase 3, controlled focuSSed study, it has been reported that there was a lower reduction in FVC values of TCZ group compared to the control group at the end of week 48 (42).

Tyrosine Kinase Inhibitors

1-Imatinib

Imatinib is a tyrosine kinase inhibitor which has been shown to exhibit anti-fibrotic properties by regressing tissue fibrosis in patients with SSc (43). There are a large number of case reports and two small-scale observational studies related to the use of imatinib in refractory SSc-ILD in the literature. Although signs of improvement were detected in pulmonary function tests as a result of observational studies, the obtained results remained controversial since a significant number of patients had to discontinue the treatment due to side effects and there was no control group in the studies (44,45).

2-Nintedanib

Nintedanib is a tyrosine kinase inhibitor that inhibits the non-receptor kinases of transforming growth factor β (TGF-β), fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor receptor (VEGFR) and Src families. Nintedanib is a drug first used in the treatment of idiopathic pulmonary fibrosis and has been shown to be effective with its antifibrotic properties (46,47). In the randomized, double-blind, placebo-controlled, Phase III SENSCIS study evaluating the efficacy and safety of nintedanib in SSc-ILD, the patients were randomized to receive nintedanib at a dose of 2 x 150 mg/day or placebo for 52 weeks (48). The decrease in FVC at week 52 was lower in the nintedanib arm. In a new study evaluating nintedanib and mycophenolate mofetil (MMF) subgroup of the SENSCIS study, no difference was detected in terms of variability of FVC values in patients who received a combination of MMF and nintedanib and those who only received MMF (49).

Antifibrotic Treatment: Pirfenidone

Pirfenidone is a drug used in the treatment of IPF due to its antifibrotic, anti-inflammatory and antioxidant properties. Although its mechanism of action is not exactly known, it is considered to act by inhibiting the TGF-β pathway and preventing proliferation of fibroblasts and differentiation into myofibroblasts. According to the results of two large-scale randomized controlled studies (CAPACITY) evaluating the efficacy of pirfenidone IPF patients, it has been reported that it had a positive effect on respiratory parameters compared to placebo (50). In a randomized, open-label, Phase II trial (LOTUSS Trial) evaluating the effect of pirfenidone in patients with SSc-ILD, no significant difference could be demonstrated between the placebo and pirfenidone arms (51). Miura et al. have used pirfenidone in five patients with SSc-ILD and have reported that pirfenidone had positive effects on vital capacity (52). In a recent randomized, double-blind, placebo-controlled pilot study, it has been reported that there was no significant or positive difference between pirfenidone and placebo in terms of their effects on FVC values at the end of six months of treatment of SSc-ILD (53).

Hematopoietic Stem Cell

Hematopoietic stem cell transplantation (HSCT) has become a promising treatment option in recent years in patients with severe and progressive SSc-ILD who are resistant to conventional treatments. In the multicenter, randomized controlled, phase 3 SCOT study evaluating HSCT treatment in patients with SSc-ILD, survival in patients in the HSCT group and improvement in FVC at the end of 54 months were demonstrated to be better compared to the control group (54). In addition, patients who received HSCT treatment had less worsening in their disease and more improvement was observed in HSCT compared to the

control group. Autologous Stem Cell Transplantation International Scleroderma (ASTIS) study was the first randomized controlled, phase 3 study in which HSCT treatment was compared with monthly cyclophosphamide treatment (55). In this multicenter study, mortality in the first year was higher in the HSCT group while survival at a median follow-up of 5.8 years was better in the HSCT group than the cyclophosphamide group. Although statistical significance was not reached at the end of the study, the FVC and DLCO values were less impaired in the HSCT group. Large-scale studies with a high number of patients and results are needed to demonstrate the efficacy and safety of HSCT in SSc-ILD patients.

Lung Transplantation

Lung transplantation could be a treatment option for selected SSc-ILD patients who have progressive disease despite drug therapies administered. This treatment option may be tried in well-selected patients. In a retrospective study evaluating lung transplantation in patients with SSc-ILD, mortality rate has been found to be 48% at the end of the first year (56). In several studies performed at different times, survival in SSc-ILD patients who underwent lung transplantation was similar to that of transplanted patients with fibrotic lung disease without SSc disease (57-60). There is a need for new large-scale studies to elaborate on the effects of lung transplantation on the survival of patients with SSc-ILD.

CONCLUSION

There have been promising developments in the treatment of SSc-ILD in recent years. Except for drug treatments such as cyclophosphamide, mycophenolate mofetil, rituximab and tocilizumab, HSCT and lung transplantation are treatment options which may be tried in selected patients. The studies regarding various new drugs in the experimental stage in the treatment of SSc-ILD are still ongoing and the results of these studies are expected with hope and curiosity by clinicians and patients in the near future.

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