Systemic Sclerosis Treatment

Subjects: Rheumatology

Contributor: Satoshi Ebata, Asako Yoshizaki-Ogawa, Shinichi Sato, Ayumi Yoshizaki

Systemic sclerosis (SSc) is a connective tissue disease caused by abnormal activation of the immune system. Characterized by vascular damage and fibrosis in various organs, the disease has a high frequency of complications, a poor prognosis, and high unmet medical needs.

Keywords: systemic sclerosis ; interstitial lung disease ; nintedanib ; tocilizumab ; rituximab

1. Introduction

Systemic sclerosis (SSc) is a connective tissue disease caused by abnormal activation of the immune system [1][2][3]. Characterized by vascular damage and fibrosis in various organs, the disease has a high frequency of complications, a poor prognosis, and high unmet medical needs [4][5][6][7][8].

Among the complications of SSc, potent therapeutic agents have already been found for the vascular complications of renal crisis and SSc-associated pulmonary arterial hypertension (SSc-PAH). Advances in treatment algorithms have resulted in lower mortality rates from these complications than in the past [9][10][11][12][13][14][15][16][17][18]. For renal crisis, treatment of hypertension with angiotensin-converting enzyme inhibitors has markedly improved prognosis [19]. SSc-PAH remains a difficult complication to manage, but treatment with pulmonary vasodilators early in the course of the disease has improved outcomes. A sub-analysis of the AMBITION study revealed that the combination of ambrisentan, an endothelin receptor antagonist, and tadalafil, a phosphodiesterase type 5 inhibitor, was greatly effective in the treatment of SSc-PAH [20].

In contrast, the development of sufficiently effective and safe therapies for the fibrosis symptoms caused by SSc, such as skin sclerosis and SSc-associated interstitial lung disease (SSc-ILD), has been slow and remains a major challenge [18][21][22][23]. Previously, cyclophosphamide was the only drug shown to be effective for skin sclerosis or ILD in SSc patients in a double-blind, randomized, or placebo-controlled trial [24]. However, cyclophosphamide is carcinogenic and cannot be administered long-term. The therapeutic effects of cyclophosphamide on SSc do not last for 2 years [25]. Other than cyclophosphamide, immunosuppressive therapy with methotrexate or mycophenolate mofetil may be used for fibrotic lesions in SSc. However, methotrexate failed to show significant improvements in skin sclerosis compared with the placebo in previous randomized controlled trials [26][27]. Mycophenolate mofetil was reported in the SLS II study to be not clearly different from cyclophosphamide in improving FVC for patients with SSc-ILD. However, mycophenolate mofetil failed to show superiority over cyclophosphamide in this study [28]. Additionally, the efficacy of mycophenolate mofetil has not been validated in a placebo-controlled randomized controlled trial. For these reasons, neither methotrexate nor mycophenolate mofetil is approved for SSc and is off-label when used. Autologous hematopoietic stem cell transplantation (HSCT) has been reported to significantly improve skin sclerosis and SSc-ILD compared to cyclophosphamide in open-label, randomized, and controlled trials [29][30][31][32]. However, a major problem with autologous HSCT is the high rate of treatment-related adverse events and mortality. Safety issues require careful consideration of the indications for autologous HSCT and limit the patients for whom it should be indicated [33].

Thus, treatment for skin sclerosis and ILD, important complications of SSc, has not been well established. Skin sclerosis is the most important indicator in the diagnostic criteria for SSc [34]. Its degree has been reported to correlate with poor prognosis in SSc patients [35]. In addition, SSc-ILD is the most common direct cause of death in SSc, surpassing renal crisis and SSc-PAH [4][36]. The development of therapies for fibrotic lesions in SSc is highly desirable.

2. Nintedanib

Nintedanib, an indolinone derivative, is a triple kinase inhibitor that strongly inhibits vascular endothelial growth factor receptor, fibroblast growth factor receptor, and platelet-derived growth factor receptor [37]. It suppresses fibroblast

proliferation by blocking mitogen-activated protein kinase and Akt signaling pathways in three types of cells involved in angiogenesis: endothelial cells, pericytes, and smooth muscle cells [38].

Nintedanib was first clinically applied for idiopathic pulmonary fibrosis (IPF). In the INPULSIS studies, nintedanib was shown to significantly suppress the annual rate of decrease in forced vital capacity (FVC) in patients with IPF compared with the placebo [39]. The adjusted annual rate of change in FVC was −114.7 mL in the nintedanib group and −239.9 mL in the placebo group in the INPULSIS-1 study (difference 125.3 [95% CI 77.7 to 172.8]; $p < 0.001$), and −113.6 mL in the nintedanib group and −207.3 mL in the placebo group in the INPULSIS-2 study (difference 93.7 [95% CI 44.8 to 142.7]; $p < 0.001$). This means that while nintedanib did not improve IPF, it suppressed the degree of FVC reduction by approximately half. Approved by the FDA in October 2014 for the treatment of IPF, nintedanib is recommended for conditional use in the IPF treatment guidelines of the American Thoracic Society, the European Respiratory Society, the Japanese Respiratory Society, and the Latin American Thoracic Association [40].

Having demonstrated antifibrotic effects in patients with IPF, nintedanib was subsequently investigated to expand its application in SSc, a prototype of systemic fibrosis. From 2015 to 2018, the SENSCIS study was conducted on 576 SSc-ILD patients from 32 countries [41]. Patients were randomized 1:1 to orally receive 150 mg of nintedanib twice daily or the placebo and were evaluated 52 weeks after initiation of the study drug. The adjusted annual change in FVC was −52.4 mL/year in the nintedanib group and −93.3 mL/year in the placebo group (difference 41.0 [95% CI 2.9 to 79.0]; $p = 0.04$). As with IPF, nintedanib did not improve or maintain FVC, but significantly suppressed the degree of FVC reduction. Based on the results of this study, nintedanib for SSc-ILD is now covered by insurance in many regions, with approval from the FDA in September 2019, the Japanese MHLW in December 2019, and the EMA in April 2020.

A unique aspect of the SENSCIS study was that the study drug was allowed to be administered in combination with immunosuppressive agents, such as mycophenolate mofetil. Post-hoc analyses showed that the mean adjusted annual decrease in FVC for patients taking mycophenolate mofetil at baseline was −40.2 mL in the nintedanib group and −66.5 mL in the placebo group (difference 26.3 [95% CI −27.9 to 80.6]). For patients not taking mycophenolate mofetil at baseline, the mean adjusted annual decrease in FVC was −63.9 mL in the nintedanib group and −119.3 mL in the placebo group (difference 55.4 [95% CI 2.3 to 108.5]) [42]. Nintedanib, with or without mycophenolate mofetil, demonstrated better treatment results than the placebo. When nintedanib was used in combination with mycophenolate mofetil, the degree of inhibition of FVC reduction was greater than when it was used alone. Nintedanib, an antifibrotic agent, has a different mechanism of action than the immunosuppressive agents that have been the standard treatment for SSc-ILD. It has been suggested that the combination of an antifibrotic and an immunosuppressive agent may increase the therapeutic efficacy against lung fibrosis in SSc patients.

3. Tocilizumab

Tocilizumab is a recombinant humanized antihuman interleukin 6 (IL-6) receptor monoclonal antibody that binds to the IL-6 receptor with high affinity [43]. IL-6 is a known inflammatory cytokine. For example, in rheumatoid arthritis (RA), IL-6 is produced locally in the joints, causing joint swelling and elevated C-reactive protein. Tocilizumab suppresses inflammation by inhibiting downstream signaling of IL-6 and is effective against various inflammatory diseases [43][44]. The drug is approved in many countries for RA, Castleman's disease and juvenile idiopathic arthritis, and is also expected to have therapeutic effects on giant cell arteritis, polymyalgia rheumatica, and large-vessel vasculitis [44]. Tocilizumab was also approved for severe COVID-19 treatment by the EMA in 2021 [45].

IL-6 is thought to be involved in the pathogenesis of SSc. It has been reported that serum IL-6 levels in SSc patients correlate with mRSS [46], and that peripheral blood mononuclear cells of SSc patients produce more IL-6 than those of healthy controls [47]. Among SSc patients, the elevation of serum IL-6 levels is particularly prominent in diffuse cutaneous SSc patients with an early onset of the disease, suggesting a strong influence of IL-6 in the disease progression of SSc [48].

Based on these findings, two double-blind, randomized, and placebo-controlled trials of tocilizumab for SSc were conducted. First, the FaSScinate trial was carried out between 2012 and 2015 in 87 patients with SSc in five countries (Canada, France, Germany, the United Kingdom, and the United States) [49]. Patients were randomized 1:1 to receive 162 mg of tocilizumab or the placebo subcutaneously every week. The primary endpoint of the study was the change from baseline in mRSS after 24 weeks of the study drug administration. The mRSS improved by 3.92 in the tocilizumab group and 1.22 in the placebo group, with the difference between the two groups not being statistically significant (difference −2.70 [95% CI −5.85 to 0.45]; $p = 0.09$). Subsequently, from 2015 to 2019, the FocuSSced trial was conducted on 210 SSc patients from 20 countries in Europe, North America, Latin America, and Japan [50]. As in the FaSScinate trial,

patients were randomized 1:1 to receive weekly subcutaneous 162 mg of tocilizumab or the placebo. The primary endpoint of the FocuSSced study was the change in mRSS from baseline at 48 weeks after the study drug administration. The change in mRSS was −6.14 for the tocilizumab group and −4.41 for the placebo group, with no significant difference between the two groups (difference −1.73 [95% CI −3.78–0.32]; p = 0.10). In both the FaSScinate and FocuSSced studies, there was a greater improvement in mRSS in the tocilizumab group than in the placebo group, but the difference did not reach statistical significance. The effect of tocilizumab on improving skin fibrosis in SSc patients seems promising, but it has not yet been fully validated and further studies are needed.

4. Rituximab

Rituximab is a chimeric antibody against CD20, a cell membrane molecule specifically expressed in B cells. It affects the calcium ion regulatory function of CD20, inhibiting B cell signaling and the cell cycle, thereby eliminating B cells. Antibody-dependent cell-mediated cytotoxic effects and complement-dependent cytotoxic effects are also thought to be involved in the elimination of B cells by rituximab [51].

Rituximab was originally used to treat B-cell lymphomas. In recent years, its efficacy against various auto-inflammatory diseases caused by B cells, such as RA, microscopic polyangiitis, and granulomatosis with polyangiitis, has been successively validated [52]. Although the pathogenesis of SSc remains unclear, B cells are thought to play a central role [53] [54]. Abnormal B cell function has been identified in SSc, with increased expression of CD19, which is specifically expressed in B cells [55][56]. Therefore, B-cell removal therapy with rituximab was anticipated to be beneficial in the treatment of SSc.

From 2017 to 2019, the DESIRES study was conducted in Japan with 56 SSc patients [57]. Participants were randomized 1:1 to receive either rituximab 375 mg/m^2 or the placebo intravenously for four consecutive weeks. The primary endpoint was the change in mRSS from baseline after 24 weeks of the study drug administration. The placebo group showed a 2.14 worsening of mRSS while the rituximab group improved by 6.30, indicating that mRSS was significantly improved in the rituximab group compared to the placebo group (difference −8.44 [95% CI −11.00 to 5.88]; p < 0.00001). Rituximab, in the DESIRES study, is the first SSc therapeutic agent to demonstrate efficacy in a double-blind, randomized, or placebo-controlled trial with a primary endpoint of a measure of skin sclerosis. Based on the results, rituximab was approved for SSc in Japan in September 2021. However, the DESIRES study included only Japanese patients, and rituximab has not been approved for SSc in the United States or Europe.

Rituximab is anticipated to be effective for complications besides fibrotic lesions of SSc, and is currently being tested in clinical trials outside of the DESIRES study. The RESTORE sub-study, a randomized-controlled trial, examined the effect of rituximab on SSc-PAH [58]. Although no statistically significant differences were observed in this study, there was a trend toward a more favorable change in 6-min walking distance in the rituximab group compared with the placebo group, suggesting that rituximab is a promising treatment for SSc-PAH [59]. Rituximab has also been reported to be effective against SSc-related polyarthritis in retrospective studies [60]. If the efficacy of rituximab in these complications is also validated, rituximab will considerably change the treatment strategy for SSc.

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