New Lines of Treatment of Systemic Sclerosis

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Abstract

A chronic autoimmune illness known as systemic sclerosis (SSc) has an extremely dismal prognosis. There are a number of SSc consequences, but so far, there is no cure for skin sclerosis, fibrotic lesions, or SSc-associated interstitial lung disease (SSc-ILD). However, randomized, placebo-controlled trials have shown that nintedanib, tocilizumab, and rituximab are effective and safe for SSc or SSc-ILD, respectively, since 2019. After the SENSCIS study indicated that nintedanib inhibited the loss in forced vital capacity (FVC), a measure of SSc-ILD, it was approved for use in all regions of the US, Europe, and Japan as an antifibrotic drug for SSc-ILD. Following evidence that the anti-interleukin-6 receptor antibody tocilizumab prevented a decline in FVC in the FocuSSced trial, the drug was authorized for the treatment of SSc-ILD in the US. Rituximab is an anti-CD20 antibody that was approved in Japan for the treatment of SSc after showing improvement in both FVC and the modified Rodnan skin score, a marker of skin sclerosis, in the DESIRES study. These three medications mark a turning point in the history of SSc treatment. Recent developments in SSc treatments, with an emphasis on nintedanib, tocilizumab, and rituximab, are detailed in this article.

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1. Introduction

A connective tissue illness known as systemic sclerosis (SSc) [1,2,3] is brought on by an overactive immune system. There are many unfulfilled medical demands, a poor prognosis, and frequent complications due to this disease, which is defined by fibrosis and vascular damage in multiple organs [4,5,6,7,8].

The vascular consequences of SSc, such as renal crises and SSc-associated pulmonary arterial hypertension (SSc-PAH), have already identified effective treatment drugs. Lower death rates from these complications have been observed as a result of advances in treatment strategies [9–18]. There has been a dramatic improvement in prognosis for renal crisis patients treated with angiotensin-converting enzyme inhibitors for hypertension [19]. Although SSc-PAH is still a challenging complication to manage, results have improved when pulmonary vasodilators are administered early on in the disease's progression. The combination of the endothelin receptor antagonist ambrisentan and the phosphodiesterase type 5 inhibitor tadalafil was found to be highly successful in treating SSc-PAH, according to a sub-analysis of the AMBITION research [20].

However, a significant obstacle has been the slow and ineffective development of safe treatments for fibrosis symptoms caused by SSc, such as skin sclerosis and SSc-associated interstitial lung disease (SSc-ILD) [18,21,22,23]. Prior to this study, no medicine had been demonstrated in a double-blind, randomized, or placebo-controlled trial to be efficacious in treating cutaneous sclerosis or ILD in patients with systemic sclerosis (SSc) [24]. Cyclophosphamide, on the other hand, is carcinogenic and should not be used for an extended period of time. Despite cyclophosphamide's promising therapeutic benefits on SSc, these effects go off after two years [25]. When treating fibrotic lesions in SSc, immunosuppressive medication with methotrexate or mycophenolate mofetil is an option in addition to cyclophosphamide. Previous randomized controlled trials [26,27] compared methotrexate to a placebo and found no significant improvement in skin sclerosis. In the SLS II trial, mycophenolate mofetil was found to improve FVC for SSc-ILD patients in a manner similar to that of cyclophosphamide. The results of this study did not favor mycophenolate mofetil over cyclophosphamide, albeit [28]. Furthermore, a placebo-controlled randomized controlled trial has not been conducted to evaluate the efficacy of mycophenolate mofetil. This is why it is considered off-label to use methotrexate or mycophenolate mofetil for SSc. Results from open-label, randomized, and controlled trials have shown that autologous hematopoietic stem cell transplantation (HSCT) is superior to cyclophosphamide in improving skin sclerosis and SSc-ILD [29,32]. Autologous HSCT has many benefits, but it also has a significant risk of treatment-related complications and death. Limiting the patients for whom autologous HSCT should be advised requires careful examination of the indications due to safety concerns [33].

Skin sclerosis and ILD are significant consequences of SSc, and treatment for these conditions is not yet well-established. The most crucial indication in the diagnostic criteria for SSc is skin sclerosis [34]. Patients with SSc are more likely to have a bad prognosis if it's severe [35]. Furthermore, after renal crisis and SSc-PAH, SSc-ILD is the leading direct cause of death in SSc [4,36]. It is extremely desirable to find treatments for fibrotic lesions in SSc.

Results from a number of nintedanib, tocilizumab, and rituximab studies that were randomized, controlled, and double-blind were published after 2019 in this context. Following the SENSCIS study's approval in September 2019, nintedanib for SSc-ILD has been consecutively approved by the European Medicines Agency (EMA), the Japanese Ministry of Health, Labor, and Welfare (MHLW), and the United States Food and Drug Administration (FDA) [37]. Next, in March 2021, tocilizumab was also approved for SSc-ILD by the FDA, based on the findings of the

FocuSSced research [38]. Consequently, rituximab for SSc was approved by the Japanese MHLW in September 2021 based on the DESIRES study's results [39].

2. Nintedanib

A triple kinase inhibitor, nintedanib is an indolinone derivative that firmly blocks the receptors for vascular endothelial growth factor, fibroblast growth factor, and platelet-derived growth factor [40]. It inhibits fibroblast growth by obstructing the signaling pathways of mitogen-activated protein kinase and Akt in three cell types implicated in angiogenesis: pericytes, endothelial cells, and smooth muscle cells [41].

Idiopathic pulmonary fibrosis (IPF) was the initial indication for the therapeutic application of nintedanib. Compared to placebo, nintedanib considerably reduced the yearly rate of decline in forced vital capacity (FVC) in patients with ischemic pulmonary fibrosis (IPF) in the INPULSIS trials [42]. In the INPULSIS-1 study, the adjusted yearly rate of change in FVC was -114.7 mL for the nintedanib group and -239.9 mL for the placebo group (difference 125.3 [95% CI 77.7 to 172.8]; $p < 0.001$). In the INPULSIS-2 study, the nintedanib group and the placebo group had a rate of change of -113.6 mL and -207.3 mL, respectively (difference 93.7 [95% CI 44.8 to 142.7]; $p< 0.001$). This indicates that nintedanib reduced the amount of FVC reduction by almost half, but it did not improve IPF. The American Thoracic Society, the European Respiratory Society, the Japanese Respiratory Society, and the Latin American Thoracic Association all advocate nintedanib for conditional use in the treatment of ischemic pulmonary fibrosis (IPF), and the drug was approved for this use by the FDA in October 2014 [43].

After nintedanib showed promise in reducing fibrosis in ischemic heart disease (IPF) patients, researchers looked into expanding its use to SSc, a model of systemic fibrosis. The SENSCIS trial included 576 SSc-ILD patients from 32 different countries and lasted from 2015 to 2018 [37]. After 52 weeks of taking the trial medicine, patients were assessed again, this time with either 150 mg of nintedanib or a placebo. The randomization was 1:1. There was a significant difference of 41.0 mL/year (95% CI 2.9 to 79.0) in the adjusted yearly change in FVC between the nintedanib group and the placebo group ($p = 0.04$). While nintedanib did not increase or preserve FVC, it did considerably reduce the amount of FVC decline, similar to IPF. With approval from the FDA in September 2019, the Japanese MHLW in December 2019, and the EMA in April 2020, nintedanib for SSc-ILD is now covered by insurance in many regions, according to this study.

The SENSCIS trial was novel in that it permitted the use of the study medicine in conjunction with immunosuppressive medications like mycophenolate mofetil. For patients starting with mycophenolate mofetil, post-hoc analyses revealed an average adjusted yearly drop of 40.2 mL in the nintedanib group and a drop of 66.5 mL in the placebo group, with a difference of 26.3 mL (95% CI –27.9 to 80.6]. The average adjusted yearly drop in FVC for patients who were not initially on mycophenolate mofetil was -63.9 mL in the nintedanib group and -119.3 mL in the placebo group, with a difference of 55.4 mL (95% CI 2.3 to 108.5) [44]. Compared to the placebo, nintedanib plus or minus mycophenolate mofetil showed superior therapeutic efficacy. The level of inhibition of FVC decline was higher when mycophenolate mofetil was administered in conjunction with nintedanib than when either drug was administered alone. The immunosuppressive drugs that have traditionally been used to treat SSc-ILD have a different

action mechanism than nintedanib, an antifibrotic drug. Some research suggests that immunosuppressive agents and antifibrotic agents may work together more effectively to treat lung fibrosis in SSc patients.

When it comes to skin fibrotic lesions, however, nintedanib does not seem to work particularly well. At 52 weeks, as a secondary endpoint of the SENSCIS trial, the modified Rodnan skin score (mRSS) changed from baseline by 2.17 in the nintedanib group and by 1.96 in the placebo group. However, there was no statistically significant difference between the two groups (difference \0.21 [95% CI –0.94 to 0.53]; p = 0.58) [37]. There was no significant difference in mRSS improvements between the nintedanib and placebo groups in either the presence or absence of mycophenolate mofetil sub-analysis. Adding an antifibrotic medication to immunosuppressive treatments may not be very beneficial for skin fibrosis. Not SSc, but SSc-ILD is the disease for which nintedanib has been approved. Alternatives to nintedanib should be the primary focus of therapy for SSc patients suffering from severe skin sclerosis.

Keep in mind that nintedanib often causes adverse effects in the digestive system. Patients treated with nintedanib in the SENSCIS trial experienced diarrhea in 75.7% of cases, nausea in 31.6%, vomiting in 24.7%, and weight loss in 11.8% of cases. All of these occurred at rates that were over two times higher than in the placebo group [37]. The nintedanib group performed worse than the placebo group on the St. George's Respiratory Questionnaire, a measure of health-related quality of life. This could be due to the increased occurrence of adverse events. In particular, a sub-analysis solely included individuals under the age of 65 found that the overall score on the St. George's Respiratory Questionnaire changed from baseline in the nintedanib group to be substantially worse than in the placebo group (difference 2.8 [95% CI 0.1 to 5.6]). It is still unclear how to control the number of side effects and the decline in quality of life that nintedanib causes. Research on individuals with ischemic bowel disease (IPF) has shown that diarrhea can be effectively managed by lowering the dosage of nintedanib or by combining it with multiple antidiarrheal medicines, like clostridium butyricum [45]. When administering nintedanib to patients with SSc-ILD, a comparable strategy might be required.

In March 2020, based on the INBUILD research [46], the FDA approved nintedanib for progressive fibrosing ILD, increasing the indication for the drug. This is a recent development outside of SSc-ILD. Like the INPULSIS and SENSCIS trials, the IMBUILD trial found that nintedanib significantly inhibited FVC decline compared to placebo. These trials have shown comparable results, which raises the possibility that nintedanib can prevent pulmonary fibrosis regardless of the underlying condition. The number of patients for whom nintedanib is advised rises due to the fact that it is available for many disorders. More data from real-world trials of nintedanib is desired in the future, regardless of SSc-ILD.

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 [47]. 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 [47,48]. 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 [48]. Tocilizumab was also approved for severe COVID-19 treatment by the EMA in 2021 [49]. 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 [50], and that peripheral blood mononuclear cells of SSc patients produce more IL-6 than those of healthy controls [51]. 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 [52]. 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) [53]. 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 [38]. 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.

In contrast, these two trials suggest that tocilizumab may be effective in patients with SSc-ILD. According to a post-hoc exploratory analysis of the FaSScinate trial, the change in FVC from baseline after 24 weeks of treatment was −34 mL in the tocilizumab group and −171 mL in the placebo group [53]. There was significantly less deterioration in FVC in the tocilizumab group compared with the placebo group (difference 136 [95% CI 9 to 264]; $p = 0.04$). However, the change in FVC from baseline after 48 weeks of treatment was −117 mL in the tocilizumab group and −237 mL in the placebo group, with no statistically significant difference between the two groups (difference 120 [95% CI 23 to 262]; $p = 0.10$). In the FocuSSced study, one of the secondary endpoints was the change from baseline in percent predicted FVC (ppFVC) at 48 weeks after the study drug administration [38]. The placebo group showed a 4.6% decrease in ppFVC, while the tocilizumab group showed only a 0.4% decrease in ppFVC. There was significantly less worsening of ppFVC in the tocilizumab group compared to the placebo group (difference 4.2 [95% CI 2.0 to 6.4]; $p = 0.0002$).

Although data from different trials cannot be simply matched, after 24 weeks of the study drug administration, nintedanib in the SENSCIS trial prevented a 44% decrease in FVC compared to the placebo [37], and tocilizumab in the FocuSSced trial prevented an 87% decrease in FVC compared to the placebo [38]. Tocilizumab may be a potent preventer of SSc-ILD progression.

Based on the results of the FocuSSced trial, in March 2021, the FDA approved tocilizumab for SSc-ILD, not SSc. However, neither the FaSScinate nor the FocuSSced trials met their primary endpoints [38,53], and tocilizumab is not currently approved for SSc-ILD in Europe or Japan. To more accurately assess the efficacy of tocilizumab in patients with SSc-ILD, it would be desirable to conduct a clinical trial with an ILD-related measure as the primary endpoint.

The safety of tocilizumab for SSc has been reported to be favorable. The three most frequently reported serious adverse events in the tocilizumab group during the 48-week double-blind period in the FocuSSced study were infections and infestations, cardiac disorders, and skin and subcutaneous tissue disorders. The incidence of all these events was rather higher in the placebo group than in the tocilizumab group [38]. The FocuSSced study included a 48-week open-label period followed by a 48-week double-blind period. During the open-label extension, all patients received tocilizumab, and no major changes in the safety profile were reported [54]. Tocilizumab may be relatively safe to use for at least the two-year treatment period.

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 [55].

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 [56]. Although the pathogenesis of SSc remains unclear, B cells are thought to play a central role [57,58]. Abnormal B cell function has been identified in SSc, with increased expression of CD19, which is specifically expressed in B cells [59,60]. 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 [39]. 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.

Not only the DESIRES trial, but also meta-analyses integrating clinical trials containing non-Asian patients have reported improvement in mRSS with rituximab treatment [61,62,63]. It is hoped that the efficacy of rituximab in fibrotic involvement of SSc will be tested in future

double-blind, placebo-controlled, and randomized controlled trials that include SSc patients from multiple ethnic groups.

After the DESIRES study was completed, a post-hoc analysis was conducted to identify patients who would benefit more from improvements in mRSS with rituximab [64]. After machine learning analysis of 27 candidate predictors, three factors were selected as determinants of the rituximab effect on mRSS improvements: baseline "peripheral blood B-cell count (≥57 μL or <57 μL)", "mRSS (≥17 or <17)", and "serum surfactant protein D (SP-D) level (≥151 ng/mL or <151 ng/mL)". The superiority of rituximab compared with the placebo was not confirmed by SSc patients with low B-cell counts. In contrast, SSc patients with high B-cell counts and high mRSS had greater improvements in mRSS with the rituximab treatment. In patients with high B-cell counts and low mRSS, serum SP-D levels affected the therapeutic effect. B cells are direct therapeutic targets with rituximab, and mRSS and serum SP-D levels are indicators reflecting the degree of skin sclerosis and SSc-ILD, respectively. B-cell removal therapy with rituximab appears to be particularly effective for SSc patients with increased B-cell counts and severe ongoing fibrosis in the skin or lungs. For SSc patients who meet these factors, it may be advisable to positively consider the use of rituximab.

In the DESIRES study, as a secondary endpoint related to SSc-ILD, the change in ppFVC from baseline after 24 weeks of the study drug administration was evaluated [39]. The placebo group had a 2.87% worsening of ppFVC while the rituximab group had a 0.09% improvement in ppFVC, with the rituximab group having significantly better ppFVC than the placebo group (difference 2.96 [95% CI 0.08–5.84]; $p < 0.04$). It is noteworthy that in the DESIRES study, unlike the SENSCIS, FaSScinate, and FocuSSced studies, FVC did not worsen in the actual drug group [37,38,39,53]. In addition, a 24-week open-label extension study in which all patients received rituximab after the double-blind phase of the DESIRES study demonstrated sustained improvements in ppFVC [65]. Rituximab was suggested to be effective in improving SSc-ILD.

The DESIRES trial also confirmed that rituximab is safe for SSc patients. During the 24-week double-blind phase, there was no significant increase in adverse events, including infections, in the rituximab group compared with the placebo group [39]. A subsequent 24-week open-label extension study did not change the safety profile, suggesting that treatment with rituximab is relatively safe for at least two courses and up to 48 weeks [65].

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 [66]. 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 [67]. Rituximab has also been reported to be effective against SSc-related polyarthritis in retrospective studies [68]. If the efficacy of rituximab in these complications is also validated, rituximab will considerably change the treatment strategy for SSc.

However, there are many unknowns about the safety of rituximab in the COVID-19 era. The DESIRES trial ended in 2019 [39,65], so the risk of COVID-19 has not been assessed. There is concern that B-cell elimination therapy with rituximab may worsen the prognosis of COVID-19

[69,70,71,72,73,74]. In SSc patients requiring rituximab, it is more important to take thorough infection control measures, such as hand washing and wearing masks [74]. In addition, the administration of rituximab may decrease the efficacy of the COVID-19 vaccine [72- 81]. Therefore, it is preferable to administer the COVID-19 vaccine before the first dose of rituximab [74]. The timing of the COVID-19 vaccination and rituximab treatment should be judged comprehensively based on the prevalence of COVID-19 and the disease status of each SSc patient. Until the COVID-19 era settles down, the appropriateness of the RTX introduction should be carefully determined.

5. Conclusions

Therapeutic agents for SSc complications, especially the fibrotic lesions, such as skin sclerosis and ILD, have been limited to date. However, since 2019, based on the results of the SENSCIS, FocuSSced, and DESIRES studies, nintedanib, tocilizumab, and rituximab have been approved in some major countries for SSc or SSc-ILD, respectively.

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