Epidemiology and Treatment of Systemic Sclerosis in Korea

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Systemic sclerosis (SSc), a rare, chronic progressive systemic autoimmune disease of unknown etiology, is characterized by autoimmunity, tissue fibrosis, and obliterative vasculopathy. SSc can affect all major organs including the skin, blood vessels, lung, heart, kidneys, and gastrointestinal tract. Our understanding of its pathogenesis has increased over the past few decades, leading to improved diagnosis and treatment. However, the mortality rate of SSc remains considerable, mainly due to cardiopulmonary causes. A growing body of evidence suggests that geographical, regional, and ethnic differences could affect the epidemiology, clinical characteristics and prognosis of SSc. Although Korean data of this issue are lacking, a considerable amount of research has been published by many Korean researchers. To establish treatment strategies for Korean patients, extensive Korean research data are needed. This review summarizes the prevalence, incidence, mortality, and clinical and laboratory manifestations of Korean patients with SSc and discusses the current trends in evidence-based treatment and recommendations.

Keywords: Systemic scleroderma, Epidemiology, Korea, Drug therapy

INTRODUCTION

Systemic sclerosis (SSc) is a rare, chronic progressive systemic autoimmune disease of unknown etiology, characterized by a wide spectrum of clinical manifestations and marked patient-to-patient variability in disease course and outcome. Its pathogenesis includes vasculopathy, immune dysregulation, and generalized fibrosis of the skin and internal organs. Microvascular injury, considered the earliest event in SSc progression, progresses to obliterative vasculopathy, predominantly affecting microvessels, resulting in tissue hypoxia, oxidative stress, and vascular complications such as Raynaud's phenomenon (RP), digital ulcer (DU), and pulmonary arterial hypertension (PAH). Immune dysregulation is characterized by innate and adaptive immune cell activation, overproduction of inflammatory cytokines and growth factors, and development of disease-specific autoantibodies, such as anti-Scl70 and anti-centromere antibody (ACA), which are presumed to play a role in linking vasculopathy and fibrosis. Fibrosis that results from excessive tissue deposition of the extracellular matrix produced by activated myofibroblasts is regarded as a distinguishing hallmark of SSc and can manifest as skin thickening and pulmonary fibrosis and gradually progress to an irreversible stage. Despite tremendous efforts in the past, there is still a lack of effective treatments to modify the progression of SSc, which poses a significant clinical burden.

Diagnosis and classification of SSc can be challenging owing to the heterogeneous nature of its pathophysiology, clinical manifestations, and disease course. To date, various classification criteria for SSc have been published. In 1980, preliminary criteria for the classification of SSc were proposed by the American Rheumatism Association (ARA) [1], known as the

American College of Rheumatology (ACR) criteria, but it has a limitation in classifying the early stages of SSc. More recently, the ACR and European League Against Rheumatism (EULAR) collaboratively developed the 2013 classification criteria for SSc, which has superior sensitivity and specificity compared with the previous 1980 ARA preliminary criteria [2]. The classification proposed by LeRoy et al. [3] in 1988, that was further revised by LeRoy and Medsger [4] in 2001, categorized SSc as limited SSc, limited cutaneous SSc (lcSSc), and diffuse cutaneous SSc (dcSSc), of which the latter two were classified according to the extent of skin fibrosis.

A growing body of evidence suggests that geographical, regional, and ethnic differences could affect the prevalence, incidence, frequency and severity of organ involvement, and mortality in SSc [5]. Herein, we discuss the epidemiological features and treatment of SSc in Korea compared to that in other countries or regions.

MAIN SUBJECTS

Prevalence, incidence and mortality

We identified two studies that reported the prevalence of SSc in Korean patients (Table 1) [6,7]. In these studies, the prevalence of SSc in Korea was 7.8 per 100,000 persons and 7.1 per 100,000 persons. Since both studies were performed using the same case definition (1980 ACR preliminary criteria) and data source (the Korean Rare Intractable Disease registry database linked to the Korean National Health Insurance database), a similar prevalence was observed. In previous studies, the prevalence of SSc varied from 3.1 to 144.5 per 100,000 persons according to case definition, country, ethnicity, and calendar period [8]. A recent meta-analysis by Bairkdar et al. [8] reported that the overall prevalence of SSc was 17.6 (95% confidence interval [CI] 15.1~20.5) per 100,000 persons. In this meta-analysis, the pooled prevalence of SSc in Asia (6.8 per 100,000 persons) was lower than that in Europe (14.8 per 100,000 persons), North America (25.9 per 100,000 persons), and Oceania

(23.8 per 100,000 persons) [8]. Only one study has described the incidence of SSc in the Korean population [6]. The incidence of SSc in South Korea is 0.8 per 100,000 person-years [6]. The overall pooled incidence of SSc was reported to be 1.4 (95% CI 1.1~1.9) per 100,000 person-years [8]. The pooled incidence of SSc in Asia, Europe, and North America was 0.9 per 100,000 person-years, 1.6 per 100,000 person-years, and 2.0 per 100,000 person-years, respectively [8]. Taken together, the prevalence and incidence of SSc in Korea seemed to be lower than those in Western countries. Since the estimated prevalence and incidence can increase when the 2013 ACR/EULAR classification criteria are applied instead of the 1980 ACR preliminary criteria, as reported in previous papers [8,9], further studies using the 2013 ACR/EULAR classification criteria are needed to estimate the prevalence and incidence of SSc in Korean patients more accurately.

The results of three Korean studies investigating the mortality associated with SSc are summarized in Table 2 [5,6,10]. The 5-year survival rate of Korean patients with SSc ranged from 85.4% to 94%. In a study by Kang et al. [6], the standardized mortality ratio (SMR) of Korean patients with SSc was 4.34, and SSc-related death was the most common cause of death. Older age, dcSSc, anti-Scl70 antibody, cardiovascular diseases (CVDs), and a forced vital capacity (FVC) less than 70% were reported to be significant risk factors for death in Korean patients with SSc [5,10]. The overall SMR of patients with SSc in previous meta-analyses was as follows: SMR=3.53 in 9 studies by Elhai et al. [11]; SMR=3.51 in 7 studies by Tolenado et al. [12]; SMR=2.72 in 17 studies by Rubio-Rivas et al. [13]. Although the survival rate has improved over the last few decades, the SMR of patients with SSc is consistently elevated [14]. The estimated cumulative 5-year survival rate after a diagnosis of SSc was reported to be 74.9% in a 2014 meta-analysis by Rubio-Rivas et al. [13], which is lower than that reported in Korean cohort. Three Korean studies used prevalent cohorts, but those could underestimate the mortality rate because they could not capture death at the very early stage of SSc [14]. Therefore, it is necessary to evaluate

Table 1. Prevalence and incidence of patients with systemic sclerosis in Korea

Author	Year	Case definition	Prevalence	Prevalence calendar year	Incidence	Incidence calendar year
Kang et al. [6]	2018	1980 ACR preliminary criteria	7.8 per 100,000	2013	0.8 per 100,000 PY	2008~2013
Kim et al. [7]	2020	1980 ACR preliminary criteria	7.1 per 100,000	2016	NA	NA

ACR: American College of Rheumatology, PY: person-years, NA: not available.

Table 2. Mortality of patients with systemic sclerosis in Korea

Author	Year	Number of patients	5-year survival rate	Follow-up period	Average annual mortality rate	SMR	Major cause of death	Risk factors for death
Kim et al. [10]	2010	243	85.4%	1972~2007	NA	NA	NA	Old age at onset, diffuse cutaneous SSc, anti-Scl70 antibody, FVC <70%, heart involvement
Kang et al. [6]	2018	4,306	88.5%	2008~2013	1.4 per 1,000,000	4.34	SSc, respiratory diseases, CV diseases	NA
Moon et al. [5]	2018	751	94%	1986~2016	NA	NA	NA	Aging, CV involvement, anti-Scl70 antibody

SMR: standardized mortality ratio, SSc: systemic sclerosis, FVC: forced vital capacity, CV: cardiovascular, Scl70: anti-Scl70 antibody, NA: not available.

the mortality rate in Korean patients through establishing a na-tionwide inception cohort.

SSc-related organ involvement accounts for more than half of the deaths in patients with SSc [14,15]. The leading cause of death in SSc patients has shifted from scleroderma renal crisis (SRC) to cardiopulmonary involvement such as interstitial lung disease (ILD) and pulmonary hypertension (PH) over time [14,15]. SSc-unrelated causes of mortality include malignancy, infection, and atherosclerotic CVDs [15]. These observations were also reported in a Korean study by Kang et al. [6]

Clinical and laboratory manifestations

1) Demographics

Moon et al. [5] recently reported the clinical and laboratory characteristics of 751 Korean patients with SSc from 11 uni-versity-affiliated hospitals, that corresponds to approximately one-fifth of all Korean patients. Thus, this retrospective cohort study is considered the most comprehensive study to evaluate the clinical features of Korean patients with SSc. The mean age at diagnosis was 48.9 years and the female-to-male ratio was ap-proximately 6:1 in Korean patients with SSc [5], which is similar to the results of studies on patients from other countries [16-21].

2) Skin fibrosis

Skin thickening is a key clinical feature of SSc, and its extent is considered a surrogate marker of disease activity and sever-ity [22]. It is generally accepted that the natural course of skin thickening differs between lcSSc and dcSSc [23]. In dcSSc, skin thickening increases rapidly in the early stage, peaks at 12~18

months, and then decreases slowly [23,24]. Compared to dcSSc, both the rate and maximum degree of skin thickening were low-er in lcSSc [23]. The modified Rodnan skin score (mRSS) is the gold standard and most widely used measure of skin thickening in patients with SSc [22]. Although there is substantial inter- and intra-rater variability in the assessment of the mRSS, it can be reduced through education and training programs [24,25]. Since its applicability is limited to the early and mild stages of skin fibrosis [22], mRSS is considered as a validated clinical outcome for dcSSc rather than for lcSSc [24]. Notably, evidence has suggested that changes in the mRSS are more closely related to functional ability, global severity, internal organ involvement, and mortality in patients with dcSSc compared with the mRSS itself [26-28]. The mean mRSS of patients with dcSSc and lc-SSc in Korea was 13.2 and 4.3, respectively [5]. In the EULAR Scleroderma Trials and Research group database, the largest registry of SSc patients worldwide, the mean mRSS of dcSSc and lcSSc were 19 and 8.1, respectively [29]. These findings sug-gest substantial differences in the mRSS among different ethnic groups, as pointed out by Khanna et al. [24]

3) Interstitial lung disease

ILD is associated with significant morbidity and mortality in patients with SSc [30]. The prevalence of ILD in SSc varies between 20% to 60% according to the definition of ILD, study design, and ethnicity [5,31]. Non-specific interstitial pneumonia is the most frequent pattern of SSc-ILD, followed by usual inter-stitial pneumonia [31]. The risk factors for ILD include the male sex, dcSSc, anti-Scl70 antibody, and African American ethnicity [32-34]. In Korean patients with SSc, the frequency of ILD was

52.7% [5], and anti-Scl70 antibody, concomitant PH, platelet count, and erythrocyte sedimentation rate were significantly associated with the presence of ILD [35]. The risk of developing ILD in patients with SSc is highest during the early course of the disease [36], but there is a high variability in the natural course of SSc-ILD. SSc-ILD can rapidly progress to an irreversible stage and result in respiratory failure, while some patients have a stable or slow progression of disease [37]. A decline in the FVC by ≥10% or a decline of 5% to 10% in FVC with a decline of ≥10% in the diffusion capacity of the lungs for carbon monoxide (DL_{CO}) is the most widely used criterion for evaluating the progression of SSc-ILD [38]. Since the progression of SSc-ILD is significantly predictive of mortality [39], early detection and screening of patients at a high risk of progression is important. A higher extent of ILD on high-resolution computed tomography (HRCT), a lower baseline FVC and/or DL_{CO}, older age, positive anti-Scl70 antibody, and negative ACA are known risk factors for the progression of SSc-ILD [30,38-41]. The Krebs von den Lungen-6 (KL-6) antigen, surfactant protein D, and chemokine ligand 18 are now recognized as biomarkers for predicting the severity, diagnosis, and prognosis of SSc-ILD, respectively [42]. In Korean patients, an association between serum KL-6 levels and the severity of semiquantitative HRCT grading and pulmonary function test parameters was found in connective tissue disease-ILD, including SSc-ILD [43].

4) Raynaud phenomenon and digital ulcer

Digital vascular diseases, including RP and DU, are common clinical manifestations of SSc [44]. As RP develops in nearly all patients with SSc, even before overt skin thickening occurs, it can be an important clue for early diagnosis. Approximately half of patients with SSc eventually experience DU, which can be persistent, recurrent, and refractory to intervention [44]. DU can progress to digital ischemia, infection, gangrene, and even digit loss and amputation, contributing to considerable pain, functional disability, and morbidity [44]. In addition, DU is reported to be a sentinel sign of internal organ involvement such as ILD, gastrointestinal (GI) involvement, and cardiac diseases [45]. History of DU, higher mRSS, younger age of onset, and longer RP and disease duration are significantly clinically associated with DU [45]. In addition, increased insulin resistance [46], serum uric acid level [47], platelet-to-lymphocyte ratio [48], neutrophil-to-lymphocyte ratio [48] and monocyte-to-high density lipoprotein cholesterol ratio [49] and vitamin D

deficiency [50] were found to be associated with the presence of DU in Korean patients with SSc.

5) Pulmonary hypertension

PH is a heterogeneous disorder defined by increased mean pulmonary arterial pressure (mPAP), and is recognized as a cardinal clinical feature of SSc. PH is further classified into the following five groups: Group 1, PAH; Group 2, PH due to left heart disease (PH-LHD); Group 3, PH due to lung diseases and/or hypoxia (PH-lung); Group 4, PH due to pulmonary artery obstructions; Group 5, PH with unclear and/or multifactorial mechanisms. The overall estimated prevalence of PH in patients with SSc was 6.4% in a recent meta-analysis (the prevalence of PH in lcSSc and dcSSc was 7.7% and 6.3%, respectively) [51]. In a nationwide multicenter retrospective cohort study, the frequency of PH in Korean patients with SSc was reported to be 13.6% [5]. Yoo et al. [52] reported that the frequency of PAH confirmed by right heart catheterization (RHC) in Korean SSc patients was 10.8% in a single-center study. Thus, the prevalence of PH in Korean patients seems to be higher than that reported in the previous meta-analysis [51]. In SSc, PAH (Group 1) and other types of PH can develop during the course of the disease [53]. In a previous meta-analysis, PAH accounted for 63% of PH in SSc, whereas the remaining 36% was secondary to ILD (Group 2) [54]. Currently known risk factors for PAH in SSc include age ≥60 years, male sex, DU, ACA, dcSSc, worse functional capacity, low DL_{CO}, and systolic blood pressure ≤110 mmHg [55-59]. SSc-associated PAH has a worse prognosis than idiopathic PAH [55] and the pooled 3-year survival rate in SSc-PAH was 52% in a previous meta-analysis [60]. Thus, early screening and prevention of PAH are crucial for optimizing the clinical outcomes of SSc. Six min walking test, N-terminal fragment brain natriuretic peptide (NTproBNP), serum uric acid level, echocardiography, and pulmonary function test are considered screening methods for SSc-PAH [55]. The DETECT algorithm is a 2-step screening model for detecting SSc patients at high risk for PAH who require echocardiography [61]. In this algorithm, Step 1 consists of six non-echocardiographic variables, including FVC/DL_{CO}, telangiectasias, ACA, NTproBNP, uric acid, and right-axis deviation on electrocardiography. When the total risk score of Step 1 was >300 points, the patient was referred for echocardiography. Step 2 includes the total risk score of Step 1 and echocardiographic variables, such as the right atrium area and tricuspid regurgitant jet velocity. If the total risk score of

Step 2 exceeds 35 points, RHC is required to confirm the PAH. Choi et al. [62] found that pulmonary vascular resistance measured by echocardiography is an important determinant of PH in Korean patients with SSc.

6) Scleroderma renal crisis

SRC is a serious life-threatening complication characterized by accelerated hypertension, progressive acute kidney injury, and thrombotic microangiopathy (TMA). Proliferative and obliterative renal vasculopathy leading to glomerular ischemia and activation of the renin-angiotensin-aldosterone system are the main mechanisms of SRC [63]. A body of evidence has suggested a potential role of abnormal complement activation in the pathogenesis of SRC, especially SSc-associated TMA. The overall prevalence of SRC was 4% in a meta-analysis [64]. The prevalence of SRC in Korean patients was 2.5%, and the frequency of SRC in dcSSc was significantly higher than that in lcSSc (4.9% vs. 1.2%, p=0.002) [5]. The majority of SRC cases occur during the early course of SSc and rapid progression of skin thickening; dcSSc, anemia, pericardial effusion, and congestive heart failure are predictors for the development of SRC [65]. Although its prognosis has significantly improved because of the introduction of angiotensin-converting enzyme inhibitors (ACEi) in the 1980s, the overall SSc related mortality remains high. The cumulative mortality rate in the post-ACEi era was approximately 20% at 6 months and 50% at 10 years from the onset of SRC, which is higher than that in other organ involvements [66].

7) Gastrointestinal involvement

The GI tract is the most common organ involved in SSc and GI disease can occur in the entire tract [67]. Secondary Sjögren's syndrome (SS), gastroesophageal reflux disease, Barrett's esophagus, gastric antral vascular ectasia, gastroparesis, chronic intestinal pseudo-obstruction, small intestinal bacterial overgrowth (SIBO), pneumatosis cystoides intestinalis, and malnutrition are representative SSc-associated GI diseases [67]. Although its exact mechanism is complex and unclear, neuropathy, myopathy, and subsequent fibrosis in the GI tract may play a pivotal role in the pathogenesis of SSc-associated GI diseases [67]. Notably, severe GI involvement, such as pseudo-obstruction and malnutrition, is associated with increased mortality [68]. Lee et al. [69] reported that more than half of Korean patients with SSc had salivary gland involvement on ultrasound examination, and salivary gland fibrosis was a prominent feature in SSc compared to primary SS.

8) Autoantibodies

There is a large variability in the frequency of SSc-specific autoantibodies such as anti-Scl70 and ACA according to different ethnicities and geographic regions, as shown in Figure 1 [5,16-21,70-73]. Patients with SSc in China, Algeria, South Korea, Malaysia, and France had a higher frequency of anti-Scl70 than ACA, whereas the frequency of ACA was higher than that of anti-Scl70 in patients with SSc in Japan, Germany, Spain, Belgium, and Brazil. The frequencies of anti-Scl70 and ACA antibodies were similar in patients with SSc in the USA and Mexico. Although the exact mechanism underlying these findings is unclear, ethnic and geographic factors may affect the development of autoantibodies in SSc.

Malignancy

The results of previous meta-analyses regarding malignancy risk in SSc have demonstrated that the overall risk is 1.47 to
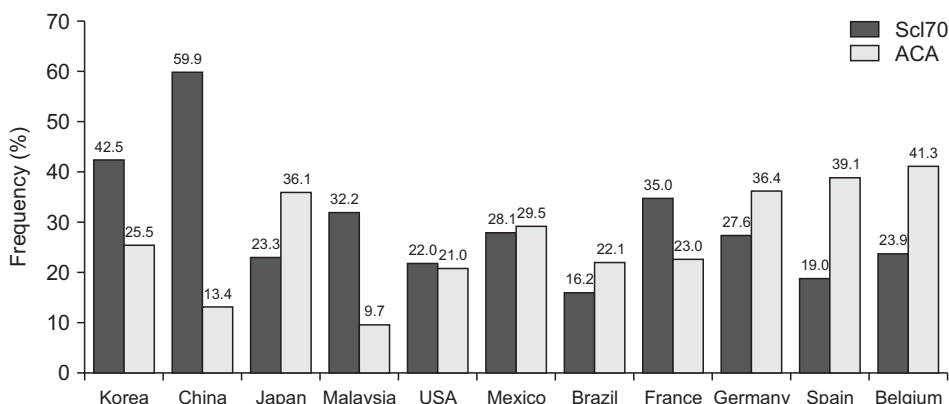
Figure 1. The frequency of systemic sclerosis specific autoantibodies in patients with systemic sclerosis according to the countries. Scl70: anti-Scl70 antibody, ACA: anti-centromere antibody.

1.75 times higher than that in the general population (Table 3). The risk of lung and hematologic malignancies in patients with SSc was significantly higher, as reported in all previous meta-analyses, whereas breast cancer risk was not significantly increased [74-76]. Kang et al. [77] reported that the overall cancer risk in Korean patients with SSc was 4.2 times higher than that in the general population. Lung cancer (23.9%) is the most common malignancy in Korean patients with SSc, followed by stomach (13%), breast (13%), and thyroid cancer (10.9%) [6]. Unexpectedly, lung cancer in Korean patients with SSc was associated with decreased mortality compared to that in individuals without rheumatic diseases, although the exact mechanism for this result is not clear [78]. Higher onset age, ILD, PH, smoking, family history of malignancy, and dcSSc are risk factors for cancer in SSc [79]. Recent evidence suggests a clinical association between SSc-specific autoantibodies and cancer. Anti-RNA polymerase III is associated with a more than 5 times higher risk of malignancies [80] and anti-Scl70 is reported to be a significant risk factor for lung cancer [81]. A negative ACA is related to an increased risk of cancer [82].

Treatment

Treatment of SSc can be challenging because of the complexity and heterogeneity of clinical manifestations, prognosis, and treatment response. Unfortunately, there is insufficient data on treatment outcomes in Korean patients with SSc. In particular, the number of randomized controlled trials (RCTs) is insufficient, and the available treatments are frequently limited by Korean National Health Insurance regulations. We discuss the treatment principles for SSc based on the results published so far, and also introduce the results from Korean patients. Treatment approach should be individualized according to each patient's condition, disease subset, stage, and organ involvement. Table 4 summarizes the medical treatments for patients with SSc based on organ involvement.

1) Skin fibrosis

The EULAR recommendations for the management of SSc recommend methotrexate (MTX) for the treatment of skin manifestations of early diffuse SSc [83]. There have been two randomized, placebo-controlled, double-blind trials on the efficacy of MTX in the treatment of skin fibrosis [84,85]. Both trials showed an improvement in the mRSS of the MTX group compared to that of the placebo group, although the result was not statistically significant. Another large observational cohort study including 326 patients with early dcSSc compared the efficacy of MTX, mycophenolate mofetil (MMF), cyclophosphamide, and no immunosuppression. Reductions in the mRSS were observed

Table 3. Results of meta-analyses analyzing the risk of malignancy in patients with systemic sclerosis

Author	Year	Malignancy	Risk
Bonifazi et al. [74]	2013	Overall	RR: 1.75 (95% CI 1.41~2.18)
		Lung cancer	RR: 4.35 (95% CI 2.08~9.09)
		Hematological neoplasms	RR: 2.24 (95% CI 1.53~3.29)
		Breast cancer	RR: 1.05 (95% CI 0.86~1.29)
Onishi et al. [75]	2013	Overall	SIR: 1.41 (95% CI 1.18~1.68)
		Lung cancer	SIR: 3.18 (95% CI 2.09~4.85)
		Hematologic malignancy	SIR: 2.57 (95% CI 1.79~3.68)
		NHL	SIR: 2.26 (95% CI 1.21~4.23)
		Leukemia	SIR: 2.75 (95% CI 1.32~5.73)
		Bladder cancer	SIR: 2 (95% CI 1.06~3.77)
		Liver cancer	SIR: 4.36 (95% CI 2~9.51)
		Breast cancer	SIR: 1.1 (95% CI 0.85~1.42)
Zhang et al. [76]	2013	Lung cancer	SIR: 3.14 (95% CI 2.02~4.89)
		NHL	SIR: 2.68 (95% CI 1.58~4.56)
		Hematopoietic cancer	SIR: 2.57 (95% CI 1.79~3.68)
		Breast cancer	SIR: 1.09 (95% CI 0.86~1.38)

RR: relative risk, CI: confidence interval, SIR: standardized incidence ratio, NHL: non-Hodgkin's lymphoma.

Table 4. Summary of medical treatment for patients with systemic sclerosis

Organ involvement	Medication
Skin fibrosis	Methotrexate
	Mycophenolate mofetil
	Cyclophosphamide
	Rituximab
Interstitial lung disease	Cyclophsophamide
	Mycophenolate mofetil
	Rituximab
	Tocilizumab
	Autologous HSCT
	Anti-fibrotic agents (nintedanib, pirfenidone)
Raynaud phenomenon and digital ulcer	Calcium channel blocker
	IV prostanoid (iloprost, epoprostenol, treprostinil)
	PDE5 inhibitor (sildenafil, tadalafil)
	ERA (bosentan, ambrisentan, macitentan)
Pulmonary arterial hypertension	PDE5 inhibitor (sildenafil, tadalafil)
	ERA (bosentan, ambrisentan, macitentan)
	Riociguat
	IV postanoid (iloprost, epoprostenol, treprostinil)
Scleroderma renal crisis	Angiotensin converting enzyme inhibitor
	Angiotensin receptor blocker
	Calcium channel blocker, alpha-blocker
	ERA (bosentan, ambrisentan, macitentan)
	Eculizumab
Gastrointestinal involvement	Proton pump inhibitor
	Prokinetic drug (metoclopramide, domperidone)
	Antibotics for SIBO (fluoroquinolone, metronidazole, tetracyclin, amoxicillin-clavulanic acid, rifaximin)

HSCT: hematopoietic stem cell transplantation, IV: intravenous, PDE5: phosphodiesterase 5, ERA: endothelin receptor antagonist, SIBO: small intestine bacterial overgrowth.

in all groups at 12 months: −4.0 (−5.2 to −2.7) for MTX, −4.1 (−5.3 to −2.9) for MMF, −3.3 (−4.9 to −1.7) for cyclophosphamide, and −2.2 (−4.0 to −0.3) for no immunosuppression. However, there was no significant difference between the therapeutic agents (p-value for between-group differences =0.346). The British Society for Rheumatology and British Health Professionals in Rheumatology guidelines suggest MMF as well as MTX for the treatment of skin involvement [86]. One observational study enrolled 25 patients with dcSSc with recent-onset (<2 years) and reported that the mRSS decreased with MMF therapy at 18.2 months [87]. Skin biopsies from three patients showed histopathological improvement and decreased expression of fibrosis-related genes. A larger retrospective analysis of 98 patients with

dcSSc treated with MMF found that an improvement in mRSS was observed as early as 3 months, and it continued through the 12-months follow-up [88]. Rituximab, an anti-CD20 monoclonal antibody, has been reported to have beneficial effects on skin involvement, but data are limited. A nested case-control study analysis of 25 patients with dcSSc treated with rituximab showed that the changes in the mRSS were larger in the rituximab group than those in the matched controls (−24.0±5.2% vs. −7.7±4.3%; p=0.03). A double-blind, RCT of 49 patients with SSc who were randomly assigned to receive rituximab or placebo reported that the absolute change in the mRSS was lower in the rituximab group (−6.3 vs. 2.15; difference −8.44, p<0.01) [89].

2) Interstitial lung disease

The EULAR recommendations for SSc-ILD suggest cyclophosphamide as the first choice despite its known toxicity [83]. The first RCT of cyclophosphamide for SSc-ILD was the Scleroderma Lung Study I (SLS I). They reported that oral cyclophosphamide had a beneficial effect on lung function, dyspnea, skin thickening, and health-related quality of life, but the effects waned after one year off therapy [90]. The second RCT compared intravenous (IV) cyclophosphamide and placebo [91]. Their regimen involved six IV pulses of cyclophosphamide combined with low-dose prednisolone followed by azathioprine. The results showed a slight improvement in the predicted FVC in the active treatment group, but there was no significant difference between the two groups. The third study was the Scleroderma Lung Study II (SLS II), comparing oral cyclophosphamide for 12 months followed by placebo with MMF for 24 months [92]. Both cyclophosphamide and MMF showed similar efficacy after 24 months, but MMF was better tolerated and was associated with less toxicity. Other recommendations or expert opinions have suggested MMF as the first or alternative agent for SSc-ILD [93]. There was a retrospective Korean study on the effect of MMF on lung function and skin thickness in 34 patients with SSc-ILD [94]. The FVC and DL_{CO} did not change significantly at 15 months, although mRSS decreased significantly from 17.5 to 10.5 after treatment with MMF. Rituximab has emerged as a potentially effective treatment option for ILD patients. A recently published meta-analysis showed that rituximab had a positive effect on lung function and skin fibrosis, but statistical significance was shown only for lung function [95]. Another emerging biologic agent for ILD is tocilizumab, a monoclonal antibody against interleukin 6 (IL-6). IL-6 is frequently elevated in patients with SSc and is known to promote inflammation and fibrotic changes via the Janus kinase 2/signal transducer and activator of transcription protein 3 pathway. The focuSSced trial, a phase 3 RCT, enrolled 210 patients with relatively early dcSSc and randomized them to receive either tocilizumab 162 mg subcutaneously per week or a placebo [96]. Tocilizumab therapy demonstrated preserved FVC over 48 weeks compared to the placebo. In addition to therapeutic agents, high-dose immunosuppression with autologous hematopoietic stem cell transplantation (HSCT) was a therapeutic option for patients with SSc and ILD. The Autologous Stem Cell Transplantation International Scleroderma trial recruited 156 patients with dcSSc from 29 centers. The HSCT group had a significantly greater improvement in the skin score and FVC than the cyclophosphamide group, but HSCT was associated with increased treatment-related mortality in the first year after treatment [97]. However, HSCT treatment showed significantly lower cumulative events after 4 years. In Korea, there has been a case report on the long-term evaluation of the efficacy of autologous HSCT. Kim et al. [98] reported the case of a 39-year-old female patient with dcSSc who developed progressive skin fibrosis despite multiple cycles of immunosuppressant treatment in the previous 6 years. She underwent autologous HSCT and showed an improvement in the mRSS from 44 to 11 after 3 years. HRCT also revealed mid-ground glass opacities in both lungs that had not changed for 3 years. Antifibrotic agents are expected to be a promising therapeutic option for managing SSc-ILD. Nintedanib, an intracellular inhibitor of tyrosine kinases, has been approved for the treatment of idiopathic pulmonary fibrosis (IPF) [99]. A large-scale international RCT was conducted to investigate the efficacy and safety of nintedanib in patients with SSc-ILD [100]. A total of 576 patients received either nintedanib or placebo for 52 weeks, and the primary endpoint was the annual rate of decline in FVC. The results showed that the annual rate of FVC decline was lower with nintedanib than with the placebo, although no clinical benefit of nintedanib was observed for other manifestations of SSc. Pirfenidone, another antifibrotic agent, has also been approved for the treatment of IPF [101]. A small-scale RCT compared the improvement in FVC in the pirfenidone and placebo groups [102]. Each group had 17 patients with SSc-ILD and were treated using stable doses of immunosupressants. They failed to demonstrate a significant beneficial effect of pirfenidone, probably because of the small number of patients. Another study of perfenidone enrolled 111 patients with CTD-ILD, 30 of whom had SSc-ILD [103]. After 24 weeks of treatment, the pirfenidone group with SSc-ILD showed a 6.60% improvement in FVC, whereas the placebo group showed a 0.55% improvement in FVC. Sometimes, a watchful waiting strategy may be a reasonable option for a subgroup of patients with stable SSc-ILD. A retrospective study enrolled 151 Korean patients with SSc-ILD and compared patients who received immunosuppressants (47.2%) with patients who did not receive immunosuppressants (53%) for a median follow-up period of 9.6 years [104]. They suggested that watchful waiting may be effective for patients with SSc-ILD who have minimal ILD on HRCT and lack PAH on echocardiography.

3) Raynaud phenomenon and digital ulcer

The management of RP and DU in SSc includes non-pharmacological, pharmacological, and surgical interventions. Non-pharmacological management includes avoidance of factors that aggravate RP, such as cold exposure, emotional stress, and vasoconstrictor drugs. Smoking cessation should be emphasized in all patients. Calcium channel blockers (CCB) are often used as first-line agents. Commonly used drugs in this class include nifedipine, felodipine, and amlodipine. A meta-analysis of CCB for RP in SSc showed that CCB can lead to significant clinical improvement in both the frequency and severity of ischemic attacks, although most studies were small clinical trials [105]. One Korean RCT compared amlodipine and udenafil, a phosphodiesterase 5 (PDE5) inhibitor, for the treatment of secondary RP [106]. They enrolled 29 patients with secondary RP associated with CTD and showed that both amlodipine and udenafil significantly decreased the rate of RP attacks. However, compared to amlodipine, udenafil improved blood flow in the digital arteries, as measured with Doppler sonography. The EULAR recommendations suggested IV iloprost as a treatment option for SSc-related DU [83]. Two RCTs revealed that IV iloprost is effective in healing DU in patients with SSc [107,108]. In addition to IV iloprost, one meta-analysis indicated that PDE5 inhibitors improved the healing of DU in patients with SSc [109]. Compared to a placebo, sildenafil, a PDE5 inhibitor, was associated with a decrease in the number of DUs at 8 and 12 weeks [110]. Tadalafil was also reported to improve the symptoms of RP and prevent new DU when used in combination with CCB [111]. Bosentan, an endothelin receptor antagonist (ERA), reduced new DU but did not affect the healing process of DU [112]. A prospective multicenter observational cohort study recruited patients with SSc-related DU from 13 hospitals in South Korea [113]. They observed 63 patients for 24 weeks and reported that ERA was more effective in reducing new DU occurrence than PDE5 inhibitor was.

4) Pulmonary hypertension

In this section, we mainly focus on treatment of PAH among PH. The main therapeutic agents for SSc-PAH are classified as PDE5 inhibitors, ERA, soluble guanylate cyclase (sGC) stimulators, and IV prostanoids. PDE5 inhibitors, including sildenafil and tadalafil, have been approved for the treatment of SSc-PAH. In the SUPER-1 trial, sildenafil improved exercise capacity, hemodynamic measures, and functional class after 12 weeks of treatment in patients with CTD-PAH [114]. Tadalafil also improved the 6-minute walk distance (6 MWD) and quality of life and reduced clinical worsening in patients with both CTD-PAH and idiopathic PAH [115]. However, treatment with tadalafil was less effective in patients with CTD-PAH than in patients with idiopathic PAH. In the ERA class, bosentan, ambrisentan, and macitentan are well-established with proven benefits. Bosentan and macitentan are nonselective oral agents that inhibit both endothelin-A and endothelin-B receptor signaling, and ambrisentan is an oral selective endothelin-A receptor antagonist. These drugs were traditionally used as monotherapy; however, recent studies have shown the benefits of combination therapy. The ambrisentan and tadalafil combination therapy was associated with a significant improvement in both right ventricular and left ventricular function, as assessed by cardiac magnetic resonance imaging in patients with SSc-PAH [116]. Riociguat, a sGC stimulator, has a dual mode of action, acting in synergy with endogenous nitric oxide and directly stimulating soluble guanylate cyclase independent of nitric oxide availability. In addition to its vasoactive properties, riociguat has been shown to have antifibrotic, antiproliferative, and anti-inflammatory effects in preclinical models [117]. Riociguat increased the mean 6 WMD, WHO functional class, pulmonary vascular resistance, and cardiac index in patients with PAH-CTD [118]. IV prostanoids approved for the treatment of SSc-PAH are epoprostenol, treprostinil, and iloprost [83]. Epoprostenol is administered intravenously because of its short half-life. Treprostinil can be administered intravenously, subcutaneously, orally, or by inhalation. Iloprost is only administered via inhalation in the US and South Korea, although an IV formulation is available in Europe. Continuous epoprostenol therapy improves exercise capacity and cardiopulmonary hemodynamics in patients with SSc-PAH [119]. Similar results were reported with IV and subcutaneous treprostinil as well as inhaled iloprost [120,121].

5) Scleroderma renal crisis

SRC is a new onset of accelerated arterial hypertension and/or rapidly progressive oliguric renal failure during scleroderma. SRC can be triggered by high doses of glucocorticoids and nephrotoxic drugs such as cyclosporine; therefore, these agents should be avoided. ACEi are the first recommended agents for the treatment of SRC. A prospective observational cohort study showed that ACEi decreased the need for dialysis and improved the survival of patients with SRC [122]. If ACEi are not tolerat-

ed, angiotensin receptor blockers are alternative agents, although they seem to be less effective than ACEi [123]. The prophylactic use of ACEi is not recommended for patients at risk of SRC because it is associated with an increased risk of SRC [124]. CCB or alpha-blockers can be used as additional therapy if blood pressure control remains suboptimal despite the maximum dose of ACEi [65]. Beta-blockers are contraindicated because of the risk of reduced cardiac output and increased peripheral resistance [125]. Recently, ERA and eculizumab, a C5-inhibitor, have been suggested as alternative therapeutic agents for refractory cases of SRC [65].

6) Gastrointestinal involvement

The GI tract is the most commonly involved internal organ in SSc, affecting nearly 50%~90% of patients. The most frequently involved site is the esophagus, followed by the ano-rectum and the small bowel. Esophageal symptoms include volume reflux, nausea, vomiting, heartburn, and dysphagia. Lee et al. [126] reported that esophageal involvement in Korean patients with SSc was characterized by heterogeneous patterns, with a higher prevalence of normal motility, and a lower prevalence of erosive esophagitis. Therefore, treatment must be tailored to each patient's condition. Lifestyle changes, such as smoking cessation, eating smaller portions more often, eating the last meal of the day earlier, and elevation of the head of the bed, should be implemented for all symptomatic patients. Proton pump inhibitors (PPIs) are the most commonly prescribed drugs in symptomatic patients. Patients who fail to respond to once-daily PPI therapy should be treated with twice-daily PPI therapy. Esophageal dysmotility can present as dysphagia or sensation of food in the throat. Prokinetic drugs are usually prescribed to treat symptomatic esophageal dysmotility. Metoclopromide is a dopamine receptor antagonist (D2) that also activates 5-hydroxytryptamine receptors for the combined effect of increased peristalsis and can increase lower esophageal sphincter tone [127]. Domperidone, another D2 antagonist, increases the tone of the inferior esophagus and peristalsis of the antrum; however, the risk of death and severe arrhythmia has been a major concern, especially at higher doses. It should be used with caution in patients with heart failure or arrhythmia. SIBO is common in SSc, affecting 33%~43% of patients [128]. The primary treatment for SIBO is antibiotic therapy. Adequate antimicrobial coverage can be achieved by using several different antibiotic regimens. Broad-spectrum antibiotics include fluoroquinolones, metronidazole, tetracycline, amoxicillin-clavulanic acid, and rifaximin [129]. Probiotics may effectively decontaminate SIBO and relieve abdominal pain but have been ineffective in preventing SIBO [130].

CONCLUSION

SSc is a highly heterogeneous autoimmune disease with a varying clinical spectrum. It is important to identify patients at risk of complications and treat them with appropriate modalities at the appropriate time. For the optimal management of Korean patients with SSc, large-scale epidemiologic data are essential, including the prevalence, incidence, clinical manifestations, treatment response, and mortality. High-quality evidence from RCTs is also needed to develop management guidelines for Korean patients with SSc. Further investigations will provide necessary data to determine successful management strategies for Korean patients with SSc.

CONFLICT OF INTEREST

S.L. has been an editorial board member since 2020, and K.W.M. has been an editorial member since 2022. But they did not involve the peer review process. Except for that, no potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

S.L. and K.W.M. drafted the manuscript and reviewed the draft manuscript. All authors approved the final manuscript.

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REFERENCES

1. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum 1980;23:581-90.

2. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis Rheum 2013;65:2737-47.

3. LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA Jr, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol 1988;15:202-5.

4. LeRoy EC, Medsger TA Jr. Criteria for the classification of early systemic sclerosis. J Rheumatol 2001;28:1573-6.

5. Moon KW, Lee SS, Lee YJ, Jun JB, Yoo SJ, Ju JH, et al. Clinical and laboratory characteristics and mortality in Korean patients with systemic sclerosis: a nationwide multicenter retrospective cohort study. J Rheumatol 2018;45:1281-8.

6. Kang GW, Jung KH, Lee YS, Kim HJ, Yoon DY, Lee SH, et al. Incidence, prevalence, mortality and causes of death in systemic sclerosis in Korea: a nationwide population-based study. Br J Dermatol 2018;178:e37-9.

7. Kim H, Cho SK, Kim JW, Jung SY, Jang EJ, Bae SC, et al. An increased disease burden of autoimmune inflammatory rheumatic diseases in Korea. Semin Arthritis Rheum 2020;50:526-33.

8. Bairkdar M, Rossides M, Westerlind H, Hesselstrand R, Arkema EV, Holmqvist M. Incidence and prevalence of systemic sclerosis globally: a comprehensive systematic review and meta-analysis. Rheumatology (Oxford) 2021;60:3121-33.

9. Andréasson K, Saxne T, Bergknut C, Hesselstrand R, Englund M. Prevalence and incidence of systemic sclerosis in southern Sweden: population-based data with case ascertainment using the 1980 ARA criteria and the proposed ACR-EULAR classification criteria. Ann Rheum Dis 2014;73:1788-92.

10. Kim J, Park SK, Moon KW, Lee EY, Lee YJ, Song YW, et al. The prognostic factors of systemic sclerosis for survival among Koreans. Clin Rheumatol 2010;29:297-302.

11. Elhai M, Meune C, Avouac J, Kahan A, Allanore Y. Trends in mortality in patients with systemic sclerosis over 40 years: a systematic review and meta-analysis of cohort studies. Rheumatology (Oxford) 2012;51:1017-26.

12. Toledano E, Candelas G, Rosales Z, Martínez Prada C, León L, Abásolo L, et al. A meta-analysis of mortality in rheumatic diseases. Reumatol Clin 2012;8:334-41.

13. Rubio-Rivas M, Royo C, Simeón CP, Corbella X, Fonollosa V. Mortality and survival in systemic sclerosis: systematic review and meta-analysis. Semin Arthritis Rheum 2014;44:208-19.

14. Poudel DR, Derk CT. Mortality and survival in systemic sclerosis: a review of recent literature. Curr Opin Rheumatol 2018;30:588-93.

15. Poudel DR, Jayakumar D, Danve A, Sehra ST, Derk CT. Determinants of mortality in systemic sclerosis: a focused review. Rheumatol Int 2018;38:1847-58.

16. Meyer OC, Fertig N, Lucas M, Somogyi N, Medsger TA Jr. Disease subsets, antinuclear antibody profile, and clinical features in 127 French and 247 US adult patients with systemic sclerosis. J Rheumatol 2007;34:104-9.

17. Hunzelmann N, Genth E, Krieg T, Lehmacher W, Melchers I, Meurer M, et al. The registry of the German Network for Systemic Scleroderma: frequency of disease subsets and patterns of organ involvement. Rheumatology (Oxford) 2008;47:1185-92.

18. Hashimoto A, Tejima S, Tono T, Suzuki M, Tanaka S, Matsui T, et al. Predictors of survival and causes of death in Japanese patients with systemic sclerosis. J Rheumatol 2011;38:1931-9.

19. Simeón-Aznar CP, Fonollosa-Plá V, Tolosa-Vilella C, Espinosa-Garriga G, Ramos-Casals M, Campillo-Grau M, et al. Registry of the Spanish network for systemic sclerosis: clinical pattern according to cutaneous subsets and immunological status. Semin Arthritis Rheum 2012;41:789-800.

20. Vanthuyne M, Smith V, De Langhe E, Van Praet J, Arat S, Depresseux G, et al. The Belgian Systemic Sclerosis Cohort: correlations between disease severity scores, cutaneous subsets, and autoantibody profile. J Rheumatol 2012;39:2127-33.

21. Sujau I, Ng CT, Sthaneshwar P, Sockalingam S, Cheah TE, Yahya F, et al. Clinical and autoantibody profile in systemic sclerosis: baseline characteristics from a West Malaysian cohort. Int J Rheum Dis 2015;18:459-65.

22. Kumánovics G, Péntek M, Bae S, Opris D, Khanna D, Furst DE, et al. Assessment of skin involvement in systemic sclerosis. Rheumatology (Oxford) 2017;56(suppl 5):v53-66.

23. Volkmann ER, Furst DE. Management of systemic sclerosis-related skin disease: a review of existing and experimental therapeutic approaches. Rheum Dis Clin North Am 2015;41:399-417.

24. Khanna D, Furst DE, Clements PJ, Allanore Y, Baron M, Czirjak L, et al. Standardization of the modified Rodnan skin score for use in clinical trials of systemic sclerosis. J Scleroderma Relat Disord 2017;2:11-8.

25. Park JW, Ahn GY, Kim JW, Park ES, Kang JH, Chang SH, et al. Impact of EUSTAR standardized training on accuracy of modified Rodnan skin score in patients with systemic sclerosis. Int J Rheum Dis 2019;22:96-102.

26. Zheng B, Nevskaya T, Baxter CA, Ramey DR, Pope JE, Baron M; Canadian Scleroderma Research Group. Changes in skin score in early diffuse cutaneous systemic sclerosis are associated with changes in global disease severity. Rheumatology (Oxford) 2020;59:398-406.

27. Wu W, Jordan S, Graf N, de Oliveira Pena J, Curram J, Allanore Y, et al. Progressive skin fibrosis is associated with a decline in lung function and worse survival in patients with diffuse cutaneous systemic sclerosis in the European Scleroderma Trials and Research (EUSTAR) cohort. Ann Rheum Dis 2019;78:648-56.

28. Domsic RT, Rodriguez-Reyna T, Lucas M, Fertig N, Medsger TA Jr. Skin thickness progression rate: a predictor of mortality and early internal organ involvement in diffuse scleroderma. Ann Rheum Dis 2011;70:104-9. Erratum in: Ann Rheum Dis 2011;70:1350.

29. Walker UA, Tyndall A, Czirják L, Denton C, Farge-Bancel D, Kowal-Bielecka O, et al. Clinical risk assessment of organ manifestations in

systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database. Ann Rheum Dis 2007;66:754-63.

30. Khanna SA, Nance JW, Suliman SA. Detection and monitoring of interstitial lung disease in patients with systemic sclerosis. Curr Rheumatol Rep 2022;24:166-73. Erratum in: Curr Rheumatol Rep 2022;24:321.

31. Panagopoulos P, Goules A, Hoffmann-Vold AM, Matteson EL, Tzioufas A. Natural history and screening of interstitial lung disease in systemic autoimmune rheumatic disorders. Ther Adv Musculoskelet Dis 2021;13:1759720X211037519.

32. Steen V. Predictors of end stage lung disease in systemic sclerosis. Ann Rheum Dis 2003;62:97-9.

33. Wangkaew S, Euathrongchit J, Wattanawittawas P, Kasitanon N, Louthrenoo W. Incidence and predictors of interstitial lung disease (ILD) in Thai patients with early systemic sclerosis: inception cohort study. Mod Rheumatol 2016;26:588-93.

34. Ashmore P, Tikly M, Wong M, Ickinger C. Interstitial lung disease in South Africans with systemic sclerosis. Rheumatol Int 2018;38:657-62.

35. Jung E, Suh CH, Kim HA, Jung JY. Clinical characteristics of systemic sclerosis with interstitial lung disease. Arch Rheumatol 2018;33:322-7.

36. Denton CP, Khanna D. Systemic sclerosis. Lancet 2017;390:1685-99.

37. Hoffmann-Vold AM, Allanore Y, Alves M, Brunborg C, Airó P, Ananieva LP, et al. Progressive interstitial lung disease in patients with systemic sclerosis-associated interstitial lung disease in the EUSTAR database. Ann Rheum Dis 2021;80:219-27.

38. Goh NS, Hoyles RK, Denton CP, Hansell DM, Renzoni EA, Maher TM, et al. Short-term pulmonary function trends are predictive of mortality in interstitial lung disease associated with systemic sclerosis. Arthritis Rheumatol 2017;69:1670-8.

39. Goh NS, Desai SR, Veeraraghavan S, Hansell DM, Copley SJ, Maher TM, et al. Interstitial lung disease in systemic sclerosis: a simple staging system. Am J Respir Crit Care Med 2008;177:1248-54.

40. Nihtyanova SI, Schreiber BE, Ong VH, Rosenberg D, Moinzadeh P, Coghlan JG, et al. Prediction of pulmonary complications and long-term survival in systemic sclerosis. Arthritis Rheumatol 2014;66:1625-35.

41. Moore OA, Goh N, Corte T, Rouse H, Hennessy O, Thakkar V, et al. Extent of disease on high-resolution computed tomography lung is a predictor of decline and mortality in systemic sclerosis-related interstitial lung disease. Rheumatology (Oxford) 2013;52:155-60.

42. Bonhomme O, André B, Gester F, de Seny D, Moermans C, Struman I, et al. Biomarkers in systemic sclerosis-associated interstitial lung disease: review of the literature. Rheumatology (Oxford) 2019;58:1534-46.

43. Lee JS, Lee EY, Ha YJ, Kang EH, Lee YJ, Song YW. Serum KL-6 levels reflect the severity of interstitial lung disease associated with connective tissue disease. Arthritis Res Ther 2019;21:58.

44. Hughes M, Allanore Y, Chung L, Pauling JD, Denton CP, Matucci-Cerinic M. Raynaud phenomenon and digital ulcers in systemic sclerosis. Nat Rev Rheumatol 2020;16:208-21. Erratum in: Nat Rev Rheumatol 2021;17:246.

45. Hughes M, Herrick AL. Digital ulcers in systemic sclerosis. Rheumatology (Oxford) 2017;56:14-25.

46. Park EK, Lee SG, Kim BH, Park JH, Lee S, Kim GT. Insulin resistance is associated with digital ulcer in patients with systemic sclerosis. Clin Exp Rheumatol 2016;34 Suppl 100:85-91.

47. Kim E, Lee HN, Kim YK, Kim GT, So MW, Ahn E, et al. Increased serum uric acid levels are associated with digital ulcers in patients with systemic sclerosis. Rheumatol Int 2019;39:255-63.

48. Kim A, Kim Y, Kim GT, Ahn E, So MW, Sohn DH, et al. Platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio as potential makers for digital ulcers and interstitial lung disease in patients with systemic sclerosis: cross-sectional analysis of data from a prospective cohort study. Rheumatol Int 2020;40:1071-9.

49. Kim HB, Kim A, Kim Y, Kim GT, Ahn E, So MW, et al. Associations of serum monocyte-to-high-density lipoprotein cholesterol ratio with digital ulcers and skin fibrosis in patients with systemic sclerosis. Scand J Rheumatol 2021;50:231-8.

50. Park EK, Park JH, Kweon SM, Kim GT, Lee SG. Vitamin D deficiency is associated with digital ulcer but not with atherosclerosis or arterial stiffness in patients with systemic sclerosis: a pilot study. Clin Rheumatol 2017;36:1325-33.

51. Rubio-Rivas M, Homs NA, Cuartero D, Corbella X. The prevalence and incidence rate of pulmonary arterial hypertension in systemic sclerosis: systematic review and meta-analysis. Autoimmun Rev 2021;20:102713.

52. Yoo SJ, Park JH, Park Y, Lee JH, Sun BJ, Kim J, et al. Prevalence of pulmonary arterial hypertension in Korean adult patients with systemic sclerosis: result of a pilot echocardiographic screening study. J Cardiovasc Ultrasound 2016;24:312-6.

53. Haque A, Kiely DG, Kovacs G, Thompson AAR, Condliffe R. Pulmonary hypertension phenotypes in patients with systemic sclerosis. Eur Respir Rev 2021;30:210053.

54. Avouac J, Airò P, Meune C, Beretta L, Dieude P, Caramaschi P, et al. Prevalence of pulmonary hypertension in systemic sclerosis in European Caucasians and metaanalysis of 5 studies. J Rheumatol 2010;37:2290-8.

55. Giucă A, Mihai C, Jurcuţ C, Gheorghiu AM, Groşeanu L, Dima A, et al. Screening for pulmonary hypertension in systemic sclerosis-a primer for cardio-rheumatology clinics. Diagnostics (Basel) 2021;11:1013.

56. Fischer A, Bull TM, Steen VD. Practical approach to screening for scleroderma-associated pulmonary arterial hypertension. Arthritis Care Res (Hoboken) 2012;64:303-10.

57. Yamane K, Ihn H, Asano Y, Yazawa N, Kubo M, Kikuchi K, et al. Clinical and laboratory features of scleroderma patients with pulmonary hypertension. Rheumatology (Oxford) 2000;39:1269-71.

58. Chung L, Farber HW, Benza R, Miller DP, Parsons L, Hassoun PM, et al. Unique predictors of mortality in patients with pulmonary arterial hypertension associated with systemic sclerosis in the REVEAL registry. Chest 2014;146:1494-504.

59. Chung L, Domsic RT, Lingala B, Alkassab F, Bolster M, Csuka ME, et al. Survival and predictors of mortality in systemic sclerosis-associated pulmonary arterial hypertension: outcomes from the pulmonary hypertension assessment and recognition of outcomes in scleroderma registry. Arthritis Care Res (Hoboken) 2014;66:489-95.

60. Lefèvre G, Dauchet L, Hachulla E, Montani D, Sobanski V, Lambert M, et al. Survival and prognostic factors in systemic sclerosis-

associated pulmonary hypertension: a systematic review and meta-analysis. Arthritis Rheum 2013;65:2412-23.

61. Coghlan JG, Denton CP, Grünig E, Bonderman D, Distler O, Khanna D, et al. Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. Ann Rheum Dis 2014;73:1340-9.

62. Choi JH, Joo SJ, Kim J. Determining the necessity for right heart catheterization in pulmonary hypertension associated with connective tissue diseases assessed by echocardiography. Int J Rheum Dis 2016;19:65-73.

63. Cole A, Ong VH, Denton CP. Renal disease and systemic sclerosis: an update on scleroderma renal crisis. Clin Rev Allergy Immunol 2022 Jun 1 [Epub]. DOI:10.1007/s12016-022-08945-x.

64. Turk M, Pope JE. The frequency of scleroderma renal crisis over time: a metaanalysis. J Rheumatol 2016;43:1350-5.

65. Zanatta E, Polito P, Favaro M, Larosa M, Marson P, Cozzi F, et al. Therapy of scleroderma renal crisis: state of the art. Autoimmun Rev 2018;17:882-9.

66. Kim H, Lefebvre F, Hoa S, Hudson M. Mortality and morbidity in scleroderma renal crisis: a systematic literature review. J Scleroderma Relat Disord 2021;6:21-36.

67. Kumar S, Singh J, Rattan S, DiMarino AJ, Cohen S, Jimenez SA. Review article: pathogenesis and clinical manifestations of gastrointestinal involvement in systemic sclerosis. Aliment Pharmacol Ther 2017;45:883-98.

68. Kaniecki T, Abdi T, McMahan ZH. A practical approach to the evaluation and management of gastrointestinal symptoms in patients with systemic sclerosis. Best Pract Res Clin Rheumatol 2021;35:101666.

69. Lee KA, Choi W, Kim J, Kim HS. High prevalence of salivary gland ultrasound abnormalities in systemic sclerosis. Joint Bone Spine 2021;88:105113.

70. Rodriguez-Reyna TS, Hinojosa-Azaola A, Martinez-Reyes C, Nuñez-Alvarez CA, Torrico-Lavayen R, García-Hernández JL, et al. Distinctive autoantibody profile in Mexican Mestizo systemic sclerosis patients. Autoimmunity 2011;44:576-84.

71. Sampaio-Barros PD, Bortoluzzo AB, Marangoni RG, Rocha LF, Del Rio AP, Samara AM, et al. Survival, causes of death, and prognostic factors in systemic sclerosis: analysis of 947 Brazilian patients. J Rheumatol 2012;39:1971-8.

72. Wang J, Assassi S, Guo G, Tu W, Wu W, Yang L, et al. Clinical and serological features of systemic sclerosis in a Chinese cohort. Clin Rheumatol 2013;32:617-21.

73. Tahiat A, Allam I, Abdessemed A, Mellal Y, Nebbab R, Ladjouze-Rezig A, et al. Autoantibody profile in a cohort of Algerian patients with systemic sclerosis. Ann Biol Clin (Paris) 2020;78:126-33.

74. Bonifazi M, Tramacere I, Pomponio G, Gabrielli B, Avvedimento EV, La Vecchia C, et al. Systemic sclerosis (scleroderma) and cancer risk: systematic review and meta-analysis of observational studies. Rheumatology (Oxford) 2013;52:143-54.

75. Onishi A, Sugiyama D, Kumagai S, Morinobu A. Cancer incidence in systemic sclerosis: meta-analysis of population-based cohort studies. Arthritis Rheum 2013;65:1913-21.

76. Zhang JQ, Wan YN, Peng WJ, Yan JW, Li BZ, Mei B, et al. The risk of cancer development in systemic sclerosis: a meta-analysis. Cancer Epidemiol 2013;37:523-7.

77. Kang KY, Yim HW, Kim IJ, Yoon JU, Ju JH, Kim HY, et al. Incidence of cancer among patients with systemic sclerosis in Korea: results from a single centre. Scand J Rheumatol 2009;38:299-303.

78. Park JK, Yang JA, Ahn EY, Chang SH, Song YW, Curtis JR, et al. Survival rates of cancer patients with and without rheumatic disease: a retrospective cohort analysis. BMC Cancer 2016;16:381.

79. Fragoulis GE, Daoussis D, Pagkopoulou E, Garyfallos A, Kitas GD, Dimitroulas T. Cancer risk in systemic sclerosis: identifying risk and managing high-risk patients. Expert Rev Clin Immunol 2020;16:1105-13

80. Shah AA, Rosen A, Hummers L, Wigley F, Casciola-Rosen L. Close temporal relationship between onset of cancer and scleroderma in patients with RNA polymerase I/III antibodies. Arthritis Rheum 2010;62:2787-95.

81. Colaci M, Giuggioli D, Sebastiani M, Manfredi A, Vacchi C, Spagnolo P, et al. Lung cancer in scleroderma: results from an Italian rheumatologic center and review of the literature. Autoimmun Rev 2013;12:374-9.

82. Igusa T, Hummers LK, Visvanathan K, Richardson C, Wigley FM, Casciola-Rosen L, et al. Autoantibodies and scleroderma phenotype define subgroups at high-risk and low-risk for cancer. Ann Rheum Dis 2018;77:1179-86.

83. Kowal-Bielecka O, Fransen J, Avouac J, Becker M, Kulak A, Allanore Y, et al. Update of EULAR recommendations for the treatment of systemic sclerosis. Ann Rheum Dis 2017;76:1327-39.

84. van den Hoogen FH, Boerbooms AM, Swaak AJ, Rasker JJ, van Lier HJ, van de Putte LB. Comparison of methotrexate with placebo in the treatment of systemic sclerosis: a 24 week randomized double-blind trial, followed by a 24 week observational trial. Br J Rheumatol 1996;35:364-72.

85. Pope JE, Bellamy N, Seibold JR, Baron M, Ellman M, Carette S, et al. A randomized, controlled trial of methotrexate versus placebo in early diffuse scleroderma. Arthritis Rheum 2001;44:1351-8.

86. Denton CP, Hughes M, Gak N, Vila J, Buch MH, Chakravarty K, et al. BSR and BHPR guideline for the treatment of systemic sclerosis. Rheumatology (Oxford) 2016;55:1906-10.

87. Mendoza FA, Nagle SJ, Lee JB, Jimenez SA. A prospective observational study of mycophenolate mofetil treatment in progressive diffuse cutaneous systemic sclerosis of recent onset. J Rheumatol 2012;39:1241-7.

88. Le EN, Wigley FM, Shah AA, Boin F, Hummers LK. Long-term experience of mycophenolate mofetil for treatment of diffuse cutaneous systemic sclerosis. Ann Rheum Dis 2011;70:1104-7.

89. Ebata S, Yoshizaki A, Oba K, Kashiwabara K, Ueda K, Uemura Y, et al. Safety and efficacy of rituximab in systemic sclerosis (DESIRES): a double-blind, investigator-initiated, randomised, placebo-controlled trial. Lancet Rheumatol 2021;3:e489-97.

90. Tashkin DP, Elashoff R, Clements PJ, Roth MD, Furst DE, Silver RM, et al. Effects of 1-year treatment with cyclophosphamide on outcomes at 2 years in scleroderma lung disease. Am J Respir Crit Care Med 2007;176:1026-34.

91. Hoyles RK, Ellis RW, Wellsbury J, Lees B, Newlands P, Goh NS, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary

fibrosis in scleroderma. Arthritis Rheum 2006;54:3962-70.

92. Tashkin DP, Roth MD, Clements PJ, Furst DE, Khanna D, Kleerup EC, et al. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. Lancet Respir Med 2016;4:708-19.

93. Fernández-Codina A, Walker KM, Pope JE; Scleroderma Algorithm Group. Treatment algorithms for systemic sclerosis according to experts. Arthritis Rheumatol 2018;70:1820-8.

94. Lee KA, Kim BY, Choi SJ, Kim SK, Kim SH, Kim HS. A real-world experience of mycophenolate mofetil for systemic sclerosis: a retrospective multicenter observational study. Arch Rheumatol 2020;35:366-75.

95. de Figueiredo Caldas MMV, de Azevedo KPM, de França Nunes AC, de Oliveira VH, Pimenta IDSF, de Araújo IDT, et al. Is rituximab effective for systemic sclerosis? A systematic review and meta-analysis. Adv Rheumatol 2021;61:15.

96. Roofeh D, Lin CJF, Goldin J, Kim GH, Furst DE, Denton CP, et al. Tocilizumab prevents progression of early systemic sclerosis-associated interstitial lung disease. Arthritis Rheumatol 2021;73:1301-10.

97. van Laar JM, Farge D, Sont JK, Naraghi K, Marjanovic Z, Larghero J, et al. Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis: a randomized clinical trial. JAMA 2014;311:2490-8.

98. Kim N, Kim JS, Choi WH, Kim KH, Lee KA, Kim HS. Long-term evaluation of autologous hematopoietic stem cell transplantation in a patient with progressive systemic sclerosis. Arch Rheumatol 2021;36:308-10.

99. Wollin L, Wex E, Pautsch A, Schnapp G, Hostettler KE, Stowasser S, et al. Mode of action of nintedanib in the treatment of idiopathic pulmonary fibrosis. Eur Respir J 2015;45:1434-45.

100. Distler O, Highland KB, Gahlemann M, Azuma A, Fischer A, Mayes MD, et al. Nintedanib for systemic sclerosis-associated interstitial lung disease. N Engl J Med 2019;380:2518-28.

101. King TE Jr, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med 2014;370:2083-92. Erratum in: N Engl J Med 2014;371:1172.

102. Acharya N, Sharma SK, Mishra D, Dhooria S, Dhir V, Jain S. Efficacy and safety of pirfenidone in systemic sclerosis-related interstitial lung disease-a randomised controlled trial. Rheumatol Int 2020;40:703-10.

103. Wang J, Wang X, Qi X, Sun Z, Zhang T, Cui Y, et al. The efficacy and safety of pirfenidone combined with immunosuppressant therapy in connective tissue disease-associated interstitial lung disease: a 24-week prospective controlled cohort study. Front Med (Lausanne) 2022;9:871861.

104. Kwon HM, Kang EH, Park JK, Go DJ, Lee EY, Song YW, et al. A decision model for the watch-and-wait strategy in systemic sclerosis-associated interstitial lung disease. Rheumatology (Oxford) 2015;54:1792-6.

105. Thompson AE, Shea B, Welch V, Fenlon D, Pope JE. Calcium-channel blockers for Raynaud's phenomenon in systemic sclerosis. Arthritis Rheum 2001;44:1841-7.

106. Lee EY, Park JK, Lee W, Kim YK, Park CS, Giles JT, et al. Head-to-head comparison of udenafil vs amlodipine in the treatment of secondary Raynaud's phenomenon: a double-blind, randomized, crossover study. Rheumatology (Oxford) 2014;53:658-64.

107. Wigley FM, Seibold JR, Wise RA, McCloskey DA, Dole WP. Intravenous iloprost treatment of Raynaud's phenomenon and ischemic ulcers secondary to systemic sclerosis. J Rheumatol 1992;19:1407-14.

108. Wigley FM, Wise RA, Seibold JR, McCloskey DA, Kujala G, Medsger TA Jr, et al. Intravenous iloprost infusion in patients with Raynaud phenomenon secondary to systemic sclerosis. A multicenter, placebo-controlled, double-blind study. Ann Intern Med 1994;120:199-206.

109. Tingey T, Shu J, Smuczek J, Pope J. Meta-analysis of healing and prevention of digital ulcers in systemic sclerosis. Arthritis Care Res (Hoboken) 2013;65:1460-71.

110. Hachulla E, Hatron PY, Carpentier P, Agard C, Chatelus E, Jego P, et al. Efficacy of sildenafil on ischaemic digital ulcer healing in systemic sclerosis: the placebo-controlled SEDUCE study. Ann Rheum Dis 2016;75:1009-15.

111. Shenoy PD, Kumar S, Jha LK, Choudhary SK, Singh U, Misra R, et al. Efficacy of tadalafil in secondary Raynaud's phenomenon resistant to vasodilator therapy: a double-blind randomized cross-over trial. Rheumatology (Oxford) 2010;49:2420-8.

112. Matucci-Cerinic M, Denton CP, Furst DE, Mayes MD, Hsu VM, Carpentier P, et al. Bosentan treatment of digital ulcers related to systemic sclerosis: results from the RAPIDS-2 randomised, double-blind, placebo-controlled trial. Ann Rheum Dis 2011;70:32-8.

113. Chang SH, Jun JB, Lee YJ, Kang TY, Moon KW, Ju JH, et al. A clinical comparison of an endothelin receptor antagonist and phosphodiesterase type 5 inhibitors for treating digital ulcers of systemic sclerosis. Rheumatology (Oxford) 2021;60:5814-9.

114. Badesch DB, Hill NS, Burgess G, Rubin LJ, Barst RJ, Galiè N, et al. Sildenafil for pulmonary arterial hypertension associated with connective tissue disease. J Rheumatol 2007;34:2417-22.

115. Galiè N, Denton CP, Dardi F, Manes A, Mazzanti G, Li B, et al. Tadalafil in idiopathic or heritable pulmonary arterial hypertension (PAH) compared to PAH associated with connective tissue disease. Int J Cardiol 2017;235:67-72.

116. Sato T, Ambale-Venkatesh B, Lima JAC, Zimmerman SL, Tedford RJ, Fujii T, et al. The impact of ambrisentan and tadalafil upfront combination therapy on cardiac function in scleroderma associated pulmonary arterial hypertension patients: cardiac magnetic resonance feature tracking study. Pulm Circ 2018;8:2045893217748307.

117. Dees C, Beyer C, Distler A, Soare A, Zhang Y, Palumbo-Zerr K, et al. Stimulators of soluble guanylate cyclase (sGC) inhibit experimental skin fibrosis of different aetiologies. Ann Rheum Dis 2015;74:1621-5.

118. Humbert M, Coghlan JG, Ghofrani HA, Grimminger F, He JG, Riemekasten G, et al. Riociguat for the treatment of pulmonary arterial hypertension associated with connective tissue disease: results from PATENT-1 and PATENT-2. Ann Rheum Dis 2017;76:422-6.

119. Badesch DB, Tapson VF, McGoon MD, Brundage BH, Rubin LJ, Wigley FM, et al. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. Ann Intern Med 2000;132:425-34.

120. Oudiz RJ, Schilz RJ, Barst RJ, Galié N, Rich S, Rubin LJ, et al. Trepro-

stinil, a prostacyclin analogue, in pulmonary arterial hypertension associated with connective tissue disease. Chest 2004;126:420-7.

121. Launay D, Hachulla E, Hatron PY, Goullard L, Onimus T, Robin S, et al. Aerosolized iloprost in CREST syndrome related pulmonary hypertension. J Rheumatol 2001;28:2252-6.

122. Steen VD, Medsger TA Jr. Long-term outcomes of scleroderma renal crisis. Ann Intern Med 2000;133:600-3.

123. Caskey FJ, Thacker EJ, Johnston PA, Barnes JN. Failure of losartan to control blood pressure in scleroderma renal crisis. Lancet 1997;349:620.

124. Gordon SM, Hughes JB, Nee R, Stitt RS, Bailey WT, Little DJ, et al. Systemic sclerosis medications and risk of scleroderma renal crisis. BMC Nephrol 2019;20:279.

125. Lynch BM, Stern EP, Ong V, Harber M, Burns A, Denton CP. UK Scleroderma Study Group (UKSSG) guidelines on the diagnosis and management of scleroderma renal crisis. Clin Exp Rheumatol 2016;34 Suppl 100:106-9.

126. Lee JS, Kim HS, Moon JR, Ryu T, Hong SJ, Cho YS, et al. Esophageal involvement and determinants of perception of esophageal symptoms among South Koreans with systemic sclerosis. J Neurogastroenterol Motil 2020;26:477-85.

127. Frech TM, Mar D. Gastrointestinal and hepatic disease in systemic sclerosis. Rheum Dis Clin North Am 2018;44:15-28.

128. Gyger G, Baron M. Gastrointestinal manifestations of scleroderma: recent progress in evaluation, pathogenesis, and management. Curr Rheumatol Rep 2012;14:22-9.

129. McFarlane IM, Bhamra MS, Kreps A, Iqbal S, Al-Ani F, Saladini-Aponte C, et al. Gastrointestinal manifestations of systemic sclerosis. Rheumatology (Sunnyvale) 2018;8:235.

130. Zhong C, Qu C, Wang B, Liang S, Zeng B. Probiotics for preventing and treating small intestinal bacterial overgrowth: a meta-analysis and systematic review of current evidence. J Clin Gastroenterol 2017;51:300-11.