Systemic sclerosis

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European expert recommendations for managing systemic sclerosis and its complications

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Check for updates

The updated 2023 EULAR recommendations for treatment of systemic sclerosis bring notable changes to recommendations for skin, peripheral vascular disease, interstitial lung disease and pulmonary arterial hypertension therapies, based on newer evidence. These updates provide the first glimmer of personalized patient management.

REFERS TO Del Galdo F. et al. EULAR recommendations for the treatment of systemic sclerosis: 2023 update. *Ann Rheum Dis*. https://doi.org/10.1136/ard-2024-226430 (2024).

Systemic sclerosis (SSc) is a rare, complex, autoimmune and connective tissue disease that can affect multiple organs. EULAR developed recommendations for the pharmacological management of SSc in 2009 and updated these recommendations in 2017. The 2023 EULAR recommendations have now been published[1].

In terms of peripheral vascular complications, few changes have been made from the 2017 guidelines in the management of Raynaud phenomenon or digital ulcers, with phosphodiesterase 5 (PDE5) inhibitors still the recommended treatment for both conditions. Iloprost is recommended for both recalcitrant Raynaud phenomenon and digital ulcers.

The 2017 guidelines recommended fluoxetine as an alternative therapy for the treatment of Raynaud phenomenon in patients with SSc and I am disheartened that it has been removed in the new guidelines. Although the supporting literature for fluoxetine is limited to one small positive randomized trial ($n = 27$) comparing fluoxetine 20 mg daily with long-acting nifedipine 40 mg daily[2], patients with SSc often have low blood pressure and are unable to tolerate vasodilating therapies, so alternatives are needed. In addition, as SSc affects predominantly perimenopausal and postmenopausal women who can suffer from hot flashes, and is associated with concurrent depression and anxiety, fluoxetine could have dual and potentially triple benefit for some patients. By removing it from the guidelines, many practitioners might not consider it any longer as an adjunctive therapy for Raynaud phenomenon, which could be a disservice to patients.

Surprisingly absent in the new guidelines was any formal assessment of botulinum toxin injection for digital ulcers or Raynaud phenomenon, despite a growing body of supportive literature.

For pulmonary arterial hypertension (PAH), the new guidelines recommend that the combination of PDE5 and endothelin receptor antagonists should be considered as first-line treatment (level 1a evidence). Another addition is the consideration of riociguat and selexipag for PAH, with a noted lower level of evidence (level 1b). Important to mention is the new recommendation against the use of warfarin in SSc-PAH, on the basis of a meta-analysis showing increased mortality with anticoagulation (HR 1.58, 95% CI 1.08–2.31; $P = 0.02$)[3], which I am glad was added. The revised guidelines were published just prior to the approval of sotatercept for PAH treatment by the FDA, the European Medicines Agency and Japan's Pharmaceuticals and Medical Devices Agency in 2024. Although its absence is conspicuous just a year later, it was appropriate not to include at the time and is a reminder of how quickly medicine can advance.

The new therapies recommended for skin management in SSc are rituximab and tocilizumab. I feel that these therapies are probably beneficial in subsets of disease based on their molecular mechanisms. The task force felt that additional evidence of efficacy of intravenous immunoglobulin for managing skin involvement in SSc was required before being included in recommendations; trials are underway.

The recommendation for rituximab was driven primarily by the outcomes of the DESIRES trial. DESIRES enrolled 59 patients in Japan, randomized 1:1 to receive rituximab or placebo[4]. This trial did not focus on early diffuse SSc; the median disease duration was nearly 5 years (58 months) in the rituximab arm and >50% of patients were positive for anti-Scl70 antibody. The change in modified Rodnan skin score (mRSS) at 24 weeks was −6.3 in the rituximab group versus +2.1 in the placebo group (difference −8.4; 95% CI −11.0 to −5.9; $P < 0{\cdot}0001$). In the open-label extension, rituximab was associated with continual decline in mRSS irrespective of original treatment group allocation[5]. A post-hoc analysis of DESIRES published after these recommendations reported that a high $CD19^+$ cell count of $\geq 57\ \mu l^{-1}$ was associated with skin response to rituximab, more so in those with higher mRSS[6]. This finding supports biological plausibility with the drug's mechanism of action and suggests a way to potentially identify responders given the risks associated with rituximab in the post-COVID world.

In a separate open-label, randomized controlled trial of early (<3 years) diffuse SSc, patients with interstitial lung disease (ILD) and positive for Scl70 were randomized to rituximab versus monthly intravenous cyclophosphamide[7]. As a secondary endpoint, mRSS at 24 weeks declined more in the rituximab group than in the cyclophosphamide group (−9.67 versus −5.5, respectively)[7]. Although SSc-associated antibodies are not generally considered to have a role in pathogenesis, antibodies to Scl70 may well be the exception, as they have been shown to bind to the surface of fibroblasts and stimulate the activation of monocytes. Given this, it seems intuitive that a medication targeting B cells might have use in patients with positivity for anti-Scl70

antibody and might have also driven the DESIRES results given the high percentage of Scl70 antibody positivity in that study.

Tocilizumab was not supported as a first-line agent for skin involvement in SSc, but the task force suggested that it be considered for early, inflammatory skin disease. In terms of mRSS change from baseline, a phase III study showed that tocilizumab showed no significant change versus placebo, and the 2024 British Society of Rheumatology guidelines for the management of SSc do not endorse tocilizumab as an option[8]. Mycophenolate mofetil can also normalize markers of early, inflammatory skin disease clinically, making it challenging to decide if and when to use tocilizumab for skin.

For the treatment of ILD, major changes in the guidelines include the addition of four new drugs — mycophenolate mofetil, rituximab, tocilizumab and nintedanib — alongside the previously recommended cyclophosphamide.

Mycophenolate mofetil was added to ILD recommendations on the basis of the Scleroderma Lung Study II results; its use is already standard of care and is acceptable background therapy for SSc-ILD clinical trials.

Rituximab was added to ILD recommendations on the basis of the results of the RECITAL phase IIb trial (rituximab versus cyclophosphamide) and DESIRES phase II trial (rituximab versus placebo), together with several smaller, open-label trials. Rituximab is viewed as an optional first-line therapy but its combination with mycophenolate was not considered for these recommendations as no high-quality supportive evidence exists.

Tocilizumab is recommended for ILD following the results of phase II and phase III trials with multiple ILD-related secondary outcomes. In the guidelines flow chart, tocilizumab is recommended as a first-line therapy for patients in the 'early, inflammatory' subset, but the wording of the guidelines do not clearly state this. No combination with mycophenolate is considered based on lack of evidence. The flow chart for SSc-ILD is at odds with general practice in the USA, as insurance companies often demand failure of mycophenolate before authorizing tocilizumab approval, which shows the reality of how companies, not the government, decide how we treat our patients. I am personally grateful for the flow chart.

Nintedanib was added as a recommendation for ILD to be used alone or in combination with mycophenolate on the basis of results from SENSCIS and its open-label extension trial, SENSCIS-ON. The flow chart suggests consideration of nintedanib if the patient is already on mycophenolate. In SENSCIS, the relative treatment effect was similar alone or in combination with mycophenolate. However, the annual rate of forced vital capacity decline was numerically greater with nintedanib alone than in those also on mycophenolate (55.4 ml per year versus 26.3 ml per year, respectively). In practice, the high frequency of diarrhoea associated with nintedanib (75%) can lead to a dose reduction to 100 mg bid for which no supportive data exist[9].

The EULAR recommendations notably differ from the American College of Rheumatology 2023 guidelines, which strongly recommend against the use of glucocorticoids in SSc-ILD owing to risk of scleroderma renal crisis (SRC)[10]. This difference might reflect differences in the US population, where the much higher prevalence of patients with anti-RNA polymerase 3 antibodies provides an increased SRC risk.

ACE inhibitors were not recommended as a preventive option for SRC in the 2023 EULAR update — just that they be used immediately at diagnosis of SRC. No changes were made for gastrointestinal management, other than a strengthening of the level of evidence of prokinetics. Similarly, methotrexate for musculoskeletal symptom management remains unchanged in both updates. A lack of sufficient evidence existed for the task force to recommend use of tocilizumab, rituximab, abatacept, intravenous immunoglobulin, JAK inhibitors or corticosteroids. The updated recommendations are relatively comprehensive, but calcinosis management, a painful and disfiguring complication, is not addressed.

I applaud the gender balance on the task force. The methodology of these recommendations is sound and I am grateful for the time and effort of the task force. In conclusion, the updated guidelines provide a nice summary framework for applying the newer evidence for management of SSc, but I hope that in the next update, more recommendations by SSc phenotype can be included.

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Competing interests

The author declares consulting agreements with AstraZeneca and Aisa Pharma.