Updated: Recommendations for systemic sclerosis

This is the lay version of the EULAR recommendations for the treatment of systemic sclerosis. The original publication can be downloaded from the EULAR website: www.eular.org.

Del Galdo F, Lescoat A, Conaghan PG, et al EULAR recommendations for the treatment of systemic sclerosis: 2023 update Annals of the Rheumatic Diseases. doi:10.1136/ard-2024-226430

Introduction

EULAR – the European Alliance of Associations for Rheumatology – gives advice to doctors, nurses, and patients about the best way to treat and manage diseases. In 2023, EULAR updated its recommendations for the treatment of systemic sclerosis. The last version of the recommendations was published in 2017, but since then there have been new treatments developed, and new evidence collected. Researchers, healthcare professionals, and patients worked together to develop this new advice. The task force included 27 people from 17 different countries.

What do we already know?

Systemic sclerosis (often shortened to SSc) is a rare connective tissue disorder. It is sometimes also called scleroderma, but strictly this refers only to skin involvement. Because other non-skin manifestations of the disease have a significant impact, the term systemic sclerosis is preferred in the EULAR recommendations.

Systemic sclerosis has both autoimmune features and vascular manifestations, and can cause tissue and vascular fibrosis in a person's skin and internal organs. Fibrosis means that excess connective tissue is laid down, causing thickening or scarring. The organs affected can vary from person to person, and this makes the disease very variable in both the symptoms it causes, and how it should be treated.

People with systemic sclerosis usually have Raynaud's phenomenon, where blood flow is reduced in the fingers and toes and the fingers turn blue, especially upon exposure to cold or any stress. They can also experience digital ulcers on their fingers, pulmonary arterial hypertension (PAH), or scleroderma renal crisis – where a sudden increase in blood pressure is associated with rapidly declining kidney function. Other manifestations include skin fibrosis or thickening, interstitial lung disease (ILD), gastrointestinal manifestations at any point along the digestive tract, and arthritis or joint pain.

What do the recommendations say?

In total, there are 22 recommendations. These are split depending on the eight main organs or systems affected, with an additional category for people with poor prognosis. The eight organ categories are Raynaud's phenomenon, digital ulcers, pulmonary arterial hypertension (PAH), scleroderma renal crisis, skin fibrosis, interstitial lung disease (ILD), gastrointestinal manifestations, and arthritis.

Each recommendation is based on the best current knowledge from studies of scientific evidence or expert opinion. The more stars a recommendation has the stronger the evidence is. However, recommendations with limited scientific evidence may be important, because the experts can have a strong opinion even when the published evidence may be lacking.

One star (*) means it is a recommendation with limited scientific evidence.

Two stars (**) means it is a recommendation with some scientific evidence.

Three stars (***) means it is a recommendation with quite a lot of scientific evidence.

Four stars (****) means it is a recommendation supported with a lot of scientific evidence.

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Recommendations

1. For people with systemic sclerosis and Raynaud's phenomenon

- **If you have Raynaud's phenomenon, your first-line therapy should be a dihydropyridine-type calcium antagonist.******
  In Raynaud's phenomenon, blood flow is reduced in the fingers and toes. If you have Raynaud's phenomenon as part of your systemic sclerosis, the first therapy you are offered should be a dihydropyridine-type calcium antagonist – usually oral nifedipine.

- **PDE5 inhibitors should also be considered.******
  There is good evidence that drugs that inhibit the PDE5 pathway, such as sildenafil, can improve Raynaud's phenomenon – both in terms of reducing how often you get attacks, and how long they last for.

- **If you have severe disease and oral therapy fails, intravenous iloprost should be considered.******
  This is a second option, if the oral therapies above do not work for you.

2. For people with systemic sclerosis and digital ulcers

- **If you have digital ulcers, PDE5 inhibitors and/or intravenous iloprost should be considered.******
  Poor blood flow to your fingertips can cause ulcers. Digital ulcers are common in systemic sclerosis. If you have digital ulcers, your healthcare team may consider one of these treatments to help heal them or sometimes combination in front of critical ischemia.

- **Bosentan should be considered to help reduce the number of new digital ulcers.******
  This recommendation applies to bosentan. It does not apply to other drugs in the same class (endothelin receptor antagonists) as there is not enough evidence for these other agents in digital ulcers.

3. For people with systemic sclerosis and pulmonary arterial hypertension

- **If you have PAH, your team should consider using readily a combination of a PDE5 inhibitor and endothelin receptor antagonist as your first-line therapy.******
  Pulmonary arterial hypertension (PAH) is complication of systemic sclerosis. It happens when fibrosis causes arteries in the lungs to narrow, raising blood pressure and putting strain on the heart. This is a big change from the recommendations that were published in 2017. It is based on new trials in people with systemic sclerosis and pulmonary arterial hypertension.

- **Intravenous epoprostenol should be considered for people with systemic sclerosis and advanced PAH.******
  If you have pulmonary arterial hypertension (PAH) in class III and IV (causing severe symptoms and physical limitations), then your healthcare team should consider whether intravenous epoprostenol might be suitable for you.

- **Other prostacyclin analogues or agonists should be considered.*****
  This include selexipag, which has shown an overall risk reductions in clinical trials for people with systemic sclerosis and pulmonary arterial hypertension, including for reducing the risk of death.

- **Riociguat can be considered.*****
  If you have systemic sclerosis and pulmonary arterial hypertension, your healthcare team can consider riociguat. Trials of this drug suggest people see an improvement in their physical function, such as how far they can walk.

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- **The use of anticoagulants (warfarin) is not recommended.****
  This is a big change from the recommendations that were published in 2017. Anticoagulants are used in people with pulmonary arterial hypertension, but they are not appropriate if your PAH is caused by systemic sclerosis. This is because there is some evidence that they can increase the risk of death in people with systemic sclerosis.

4. For people with systemic sclerosis and renal crisis

- **ACE inhibitors should be used immediately at diagnosis of scleroderma renal crisis.****
  In scleroderma renal crisis, a sudden increase in blood pressure is associated with rapidly declining kidney function. There is not a huge amount of evidence for using ACE inhibitors in scleroderma renal crisis, but it is known that they prevent the body from producing a substance that narrows blood vessels, and so they can help to lower blood pressure and preserve renal function.

- **If you are receiving glucocorticoids your blood pressure should be regular monitored to help detect scleroderma renal crisis.****
  Again, there is not a lot of evidence on this topic, but it is a good idea to have regular blood pressure monitoring if you are taking glucocorticoids (steroids) for your systemic sclerosis. This can help to make sure that your blood pressure does not get too high.

5. For people with systemic sclerosis and gastrointestinal involvement

- **If you suffer from GERD, then you may need to take a proton pump inhibitor.*****
  Proton pump inhibitors (PPI) are often used to reduce the amount of acid produced in the stomach. If you have gastro-oesophageal reflux disease (GERD) as part of your systemic sclerosis, then a PPI might help control this. This could help to prevent ulcers and strictures or scars forming where the stomach acid comes back up and irritates your oesophagus.

- **Prokinetic drugs should be considered for symptomatic motility disturbances.****
  If you have symptomatic motility disturbances related to your systemic sclerosis – where food moves too slowly through your digestive system – then a prokinetic drug might be considered. These are medicines that drugs stimulate the gastrointestinal tract to move food along more naturally.

- **The use of rotating antibiotics should be considered for the treatment of small intestinal bacterial overgrowth.***
  Small intestinal bacterial overgrowth is common in people with systemic sclerosis, and can cause diarrhoea, flatulence, abdominal pain, bloating, and early satiety. Rotating antibiotics might be used to help keep these bacterial populations under control.

6. For people with systemic sclerosis and skin fibrosis

- **Methotrexate,*** mycophenolate mofetil,*** and/or rituximab**** should be considered for skin fibrosis.**
  This is a big change from the recommendations that were published in 2017, since there has been a lot of new evidence published on rituximab. If you have skin fibrosis or thickening caused by your systemic sclerosis, your healthcare team can consider which of these drugs might work best for you.

- **Tocilizumab may be considered for skin fibrosis if you have early, inflammatory diffuse cutaneous systemic sclerosis (dcSSc).****
  This is a big change from the recommendations that were published in 2017. Tocilizumab is a biologic drug that has been investigated in trials where skin disease was the primary outcome measure in people with early, inflammatory disease. However, there isn't yet enough evidence to recommend it as a first-line treatment.

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7. For people with systemic sclerosis and interstitial lung disease

- **Mycophenolate mofetil, cyclophosphamide, or rituximab should be considered for of SSc-ILD.******
  This is a big change from the recommendations that were published in 2017, since there has been a lot of new evidence published. If you have interstitial lung disease (ILD) caused by your systemic sclerosis, your healthcare team can consider which of these drugs might work best for you with a professional agreement to support mycophenolate mofetil as a first line drug.

- **Nintedanib should be considered for SSc-ILD.******
  This is a big change from the recommendations that were published in 2017. If you have interstitial lung disease (ILD) caused by your systemic sclerosis, your healthcare team can consider whether nintedanib might work for you – and it can be used on its own, or alongside mycophenolate mofetil.

- **Tocilizumab should be considered for SSc-ILD.*****
  This is another big change from the recommendations that were published in 2017. Although there is still some evidence needed, if you have interstitial lung disease (ILD) caused by your systemic sclerosis, your healthcare team can consider whether tocilizumab might work for you.

8. For people with systemic sclerosis and musculoskeletal symptoms

- **Methotrexate should be considered for musculoskeletal involvement.***
  Joint and muscle symptoms are common in systemic sclerosis, and are often reported as being a major concern for patients. At the moment, there is not a lot of good quality evidence for using low-dose glucocorticoids, tocilizumab, or rituximab for people with joint involvement. Instead, methotrexate is recommended.

9. For people with poor prognosis

- **High-intensity immunosuppression followed by autologous HSCT may be considered for some people with early dcSSc and poor prognosis.******
  As long as you do not have advanced cardiorespiratory disease, you might be a candidate for high-intensity immunosuppression (usually including cyclophosphamide) followed by autologous haematopoietic stem cell transplantation (HSCT). This option is only suitable for some highly selected people. You would need to have early severe diffuse cutaneous disease and poor prognosis for this to be an option.

Summary

These recommendations give guidance to both patients and their healthcare teams about the best way to treat systemic sclerosis, based on the available evidence.

Recommendations with just one or two stars are based mainly on expert opinion and not backed up by studies, but these may be as important as those with three or four stars.

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