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EULAR recommendations for the treatment of systemic sclerosis: 2023 update

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ABSTRACT

Objectives To update the 2017 European Alliance of Associations for Rheumatology (EULAR) recommendations for treatment of systemic sclerosis (SSc), incorporating new evidence and therapies.

Methods An international task force was convened in line with EULAR standard operating procedures. A nominal group technique exercise was performed in two rounds to define questions underpinning a subsequent systematic literature review. The evidence derived was discussed and overarching principles, recommendations and future research agenda were iteratively developed with voting rounds.

Results The task force agreed on 22 recommendations covering 8 clinical/organ domains including Raynaud's phenomenon, digital ulcers, pulmonary arterial hypertension, scleroderma renal crisis, skin fibrosis, interstitial lung disease (ILD), gastrointestinal manifestations and arthritis. Most new recommendations are related to skin fibrosis and ILD. These included novel recommendations for the use of mycophenolate mofetil, nintedanib, rituximab and tocilizumab for the treatment of these crucial disease manifestations. The recommendations also included first-line and second-line interventions, providing increased utility for rheumatology practitioners. Important additions to the future research agenda included consideration of novel interventions for the management of vascular, musculoskeletal and gastrointestinal manifestations and calcinosis, as well as for the local management of digital ulcers.

Conclusion These updated recommendations include the first set of synthetic and biological targeted therapies recommended for key fibrotic manifestations of SSc as well as first-line combination treatment for newly diagnosed pulmonary artery hypertension and prioritise a new research agenda for the coming years.

INTRODUCTION

Systemic sclerosis (SSc) is a rare connective tissue disorder characterised by the association of autoimmune features with vascular manifestations and culminating in tissue and vascular fibrosis of the skin and internal organs, with highly variable outcomes.[1] Type and severity of organ involvement drive the heterogeneous prognosis, but overall SSc remains the rheumatic disease with the highest morbidity and mortality, despite recent improvement in survival.[2]

The high heterogeneity in the presence and severity of skin and visceral involvement is a major challenge in clinical management and trial design.[3] The only accepted clinical subsets rely on extent of skin involvement, supported by specific antibodies and reflect relative risk of internal organ involvement.[4] Because scleroderma relates specifically to the cutaneous manifestations of the disease while the overall prognosis is strongly influenced by the visceral manifestations, the term SSc is preferred to scleroderma in these recommendations.

The management of patients with SSc includes non-pharmacological and pharmacological interventions. European Alliance of Associations for Rheumatology (EULAR) recommendations for non-pharmacological interventions have been recently published.[5] In 2009, EULAR and European Scleroderma Trial and Research (EUSTAR) working group developed evidence-based, consensus-derived recommendations for the pharmacological management of SSc.[6] An update of these recommendations was published in 2017, incorporating new classification criteria, outcome measures and therapies, based on evidence reviewed up to 2014.[7] Given the substantial published evidence since that time, a new task force aimed to update the EULAR recommendations for the pharmacological management of SSc.

METHODS

The process followed the EULAR standard operating procedures for recommendations.[8] Selection of the new task force was based on EULAR guidelines of inclusivity and increased engagement of under-represented stakeholders, being gender balanced and patient inclusive. The task force included 27 members from 17 countries (online supplemental figure 1) and included 15 females. It comprised mainly rheumatologists (22), 1 health professional, 2 patient representatives, 1 librarian and 1 methodologist (PGC). As some recommendations were

likely to be unchanged, the task force also invited all experts who contributed to elaborating the 2017 recommendations to critically review the draft recommendations and manuscript.

As with the 2014 update, the selection of clinical questions relied on the engagement of the EUSTAR network (www.eustar.org). Investigators from EUSTAR-active centres were invited to respond to an online survey to prioritise the PICO questions for the systematic literature review (SLR). Each of the previous 46 PICO questions (grouped in 23 domains) was reproposed.[7] Responders had the option to approve, not approve, suggest edits or propose new questions. Survey was hosted by FDG; it remained open for 8 weeks with a reminder sent 1 week before deadline. 101 participants responded to the survey; results of the survey were fully anonymised (Google Forms). Survey results were analysed by FDG and YA and discussed in the first nominal group technique (NGT) meeting. Questions 'approved' by at least 80% of respondents were simply proposed for approval ratification by the task force. Questions approved by less than 70% of respondents were proposed for rejection ratification to the task force. All questions that received between 70% and 80% approval were discussed. 212 new or reworded questions were grouped into 31 new questions following discussion. The list of questions approved for the new SLR is provided in the SLR paper.[9]

The SLR was conducted by five young investigators from the EMEUNET network (AL, TS, YAS, JC and EB), supervised by a task force member (PGC), supported by a librarian (JE), and covering the period from 1 January 2015 to 31 March 2023. The full report of the SLR is summarised in a separate manuscript.[9] For each question, reviewers provided a summary of the up-to-date knowledge to the task force, specifying the level of evidence (LoE) (1–5) according to CEBM criteria and suggesting a preliminary grade of recommendation.[10 11]

Evidence profiles generated from the SLR were reviewed by FDG and YA, grouped according to clinical domain and compiled in a presentation. This was presented to the task force, together with the previous recommendations, in a hybrid 2-day meeting. Task force members systematically presented the evidence and voted on whether each existing recommendation should remain unchanged or not for a particular domain, with an 80% rule for approval. Recommendations left unchanged were sometimes amended for wording and grammar and reproposed for level of agreement. Recommendations to be changed were discussed until a new recommendation was agreed. The task force voted on each updated recommendation and its strength during the face-to-face meeting, where the 'at least 80% agreement' rule was applied. Draft recommendations compiled as output of the meeting were presented to the task force in an online survey to ratify agreement on the wording. A second meeting was held online for the recommendations wording that did not reach agreement in the survey. Following that meeting, a new survey was used to collect level of agreement on the revised recommendation text. Throughout the process, items discussed were prioritised for inclusion in discussion of the manuscript and/or future research agenda.

Diagrams/figures included here should be considered as graphic summaries to simplify interpretation and should always be considered in the context of the full recommendations.

RESULTS

The process described above lasted from February 2022 to May 2023 and resulted in 22 recommendations, compared with 16 in 2017. Eight clinical domains related to SSc symptoms and organ involvement were addressed, including Raynaud's phenomenon (RP), digital ulcers (DU), pulmonary arterial hypertension (PAH), scleroderma renal crisis (SRC), skin fibrosis, interstitial lung disease (ILD), gastrointestinal (GI) and musculoskeletal manifestations. The recommendations with grade and task force level of agreement are described in table 1. A graphical summary of the strength of recommendations (SoR) and intervention/drug class, grouped by clinical manifestation is shown in figure 1. As apparent by the relationships between clinical manifestations, the evidence in SSc suggests the existence of 'therapeutic continuum groups' and defines the research agenda based on clinical manifestations lacking strong evidence (figure 1).

The vascular therapeutic continuum across Raynaud's, DUs and pulmonary artery hypertension

The evidence informing this set of recommendations focuses on the same classes of drugs for the management of RP, DU disease and pulmonary artery hypertension (PAH) in SSc. Such a 'vascular therapeutic continuum' supports the existence of common disease mechanisms underpinning these clinical manifestations (figure 1).[12] The task force noted that studies focusing on the additional value of immune suppressive or specific immune targeting interventions were lacking and should be considered as a research agenda focus (box 1).

Raynaud's phenomenon

Dihydropyridine-type calcium antagonists, usually oral nifedipine, should be used as first-line therapy for SSc-RP

The SLR did not find any new evidence on the use of calcium channel blockers for the treatment of SSc-RP. The task force, therefore, unanimously agreed to keep the previous recommendation with the same strength and wording.

PDE5 inhibitors should also be considered for treatment of SSc-RP

Since the previous set of recommendations, a meta-analysis of six RCTs published between 2005 and 2012 was conducted by Roustit *et al*.[13] These RCTs included 224 patients, different double-blind designs (parallel or cross-over) and distinct PDE5 inhibitors (PDE5i), detailed in online supplemental extended results material.[13–17] The PDE5 inhibitor group showed an overall improvement in Raynaud's condition score compared with placebo (mean difference −0.46 (95% CI −0.74 to −0.147); p=0.002). Significant differences were also noted in daily frequency of RP attacks (mean difference −0.49 (95% CI −0.71 to −0.28; p<0.0001) and daily duration of RP attacks in minutes (−14.62 (−20.25 to −9); p<0.0001). The high level of evidence provided by the 2013 meta-analysis supported previous recommendations for the use of PDE5i in SSc-RP.

Intravenous iloprost should be considered for severe SSc-RP following failure of oral therapy

The SLR did not identify new publications with higher LoE on the use of Iloprost. The task force agreed to retain the previous recommendations, including the adoption of intravenous treatment as second-line following failure of oral therapy. A treatment algorithm for SSc-RP is shown in figure 2.

In the 2017 update of the recommendations, fluoxetine was included with SoR C and relatively low level of agreement (6.06).[7] During the Delphi exercise informing this update, fluoxetine was deprioritised and not included in the SLR, so no recommendation was made for or against its use.

The conflicting evidence for the effectiveness of endothelin receptor antagonists (ERAs) in treating RP led the task force to

Table 1 Updates of EULAR recommendations for the treatment of systemic sclerosis

Organ involvement	Recommendation	LoE	SoR	LoA (SD)	% LoA>8
SSc-RP	Dihydropyridine-type calcium antagonists, usually oral nifedipine, should be used as first-line therapy for SSc-RP.	1a	A	8.6 (2.4)	88
	PDE5 inhibitors should also be considered for treatment of SSc-RP.	1a	A	8.6 (2.4)	88
	Intravenous iloprost should be considered for severe SSc-RP following failure of oral therapy.	1a	A	9.0 (1.4)	80
Digital ulcers	PDE5 inhibitors and/or intravenous iloprost should be considered for the treatment of digital ulcers in patients with SSc.	1a	A	8.8 (1.9)	92
	Bosentan should be considered for reduction of number of new digital ulcers in SSc.	1a	A	8.0 (2.5)	84
SSc-PAH	Combination of PDE5i and endothelin receptor antagonists should be considered as first-line treatment of SSc PAH.*	1a	A	8.1 (2.9)	80
	Intravenous epoprostenol should be considered for the treatment of SSc patients with advanced PAH (class III and IV)	1a	A	7.7 (3.1)	76
	Other prostacyclin analogues or agonists should be considered for the treatment of SSc PAH	1b	B	7.7 (3.1)	76
	Riociguat can be considered for treatment of SSc PAH	1b	B	8.0 (2.4)	76
	The use of anticoagulants (warfarin) for the treatment of SSc-PAH is not recommended*	2a	C	8.2 (2.1)	68
Renal crisis	ACE inhibitors should be used immediately at diagnosis of scleroderma renal crisis	4	C	8.4 (2.6)	84
	SSc patients treated with glucocorticoids should have regular monitoring of blood pressure to detect scleroderma renal crisis	3	C	7.9 (3.1)	84
Gastrointestinal involvement	PPI should be considered for the treatment of SSc-GERD and prevention of oesophageal ulcers and strictures	3	B	8.3 (2.5)	84
	The use of prokinetic drugs should be considered for the treatment of symptomatic motility disturbances related to SSc	1b	C	8.0 (2.3)	72
	The use of rotating antibiotics should be considered for the treatment of small intestinal bacterial overgrowth	2b	D	7.3 (2.7)	60
Skin	Methotrexate (1B), mycophenolate mofetil (MMF) (1B) and/or rituximab (1A) should be considered for treatment of SSc skin fibrosis*	1a-b	A/B	7.6 (3.2)	72
	Tocilizumab may be considered for the treatment of skin fibrosis in patients with early, inflammatory dcSSc*	1b	C	7.2 (2.1)	60
ILD	MMF (1A), cyclophosphamide (1A) or rituximab (1A) should be considered for the treatment of SSc-ILD*	1a	A	8.1 (2.8)	88
	Nintedanib should be considered alone or in combination with MMF for the treatment of SSc-ILD*	1a	A	8.5 (2.5)	84
	Tocilizumab should be considered for the treatment of SSc-ILD*	1b	B	7.8 (2.8)	76
Poor prognosis	High-intensity immunosuppression (usually including cyclophosphamide) followed by autologous HSCT may be considered for the treatment of selected patients with early dcSSc and poor prognosis, in the absence of advanced cardiorespiratory involvement	1a	A	7.8 (2.5)	68
Musculoskeletal	Methotrexate should be considered for the treatment of musculoskeletal involvement in SSc.	2b	D	7.8 (2.7)	80

*Substantially new recommendations compared with 2017 update.
EULAR, European Alliance of Associations for Rheumatology; GERD, gastro-oesophageal reflux disease; HSCT, haematopoietic stem cell transplantation; ILD, interstitial lung disease; LoA, level of agreement; LoE, level of evidence; PAH, pulmonary artery hypertension; RP, Raynaud's phenomenon; SoR, strength of recommendation; SSc, systemic sclerosis.

not formulate any recommendation, as summarised in online supplemental extended results.[13–17]

DU disease

PDE5 inhibitors and/or intravenous iloprost should be considered for the treatment of DU in patients with SSc

The SLR did not identify any new study on the effect of intravenous Iloprost for the healing of DU with higher level of evidence compared with the 2017 recommendations.[7] On the contrary, one RCT failed to demonstrate efficacy of oral treprostinil in DU healing and prevention (see online supplemental Extended Results).[18 19]

Concerning the use of PDE5i, there was no stronger evidence compared with that already evaluated in the previous update,[7] hence the task force retained the previous recommendation.

In discussion of the SEDUCE study,[14] the task force noted the particularly high rate of DU healing; however, the analysis could not account for the effects of specialised non-pharmacological DU treatment in highly experienced centres. The non-pharmacological contribution helped inform the research agenda on this important clinical manifestation (box 1).

In view of these considerations, the task force unanimously agreed to retain the previous recommendations.

Bosentan should be considered for reduction of number of new DU in SSc

This recommendation was unchanged from 2017 since no new or higher-level evidence was identified.[7] The recommendation remains specifically for bosentan instead of being extended to the ERA class, given the negative results of two RCTs evaluating the efficacy of macitentan in more than 400 patients with SSc DU described in detail in online supplemental extended results.[17–20] A graphical summary of the recommendations on SSc-RP and DU is shown in figure 2.

Pulmonary arterial hypertension

Combination of PDE-5i and ERAs should be considered as first-line treatment of SSc-PAH

This new recommendation is supported by two independent post hoc analyses of the same RCT, the AMBITION trial.[21–23] In AMBITION, 500 participants with PAH (connective tissue

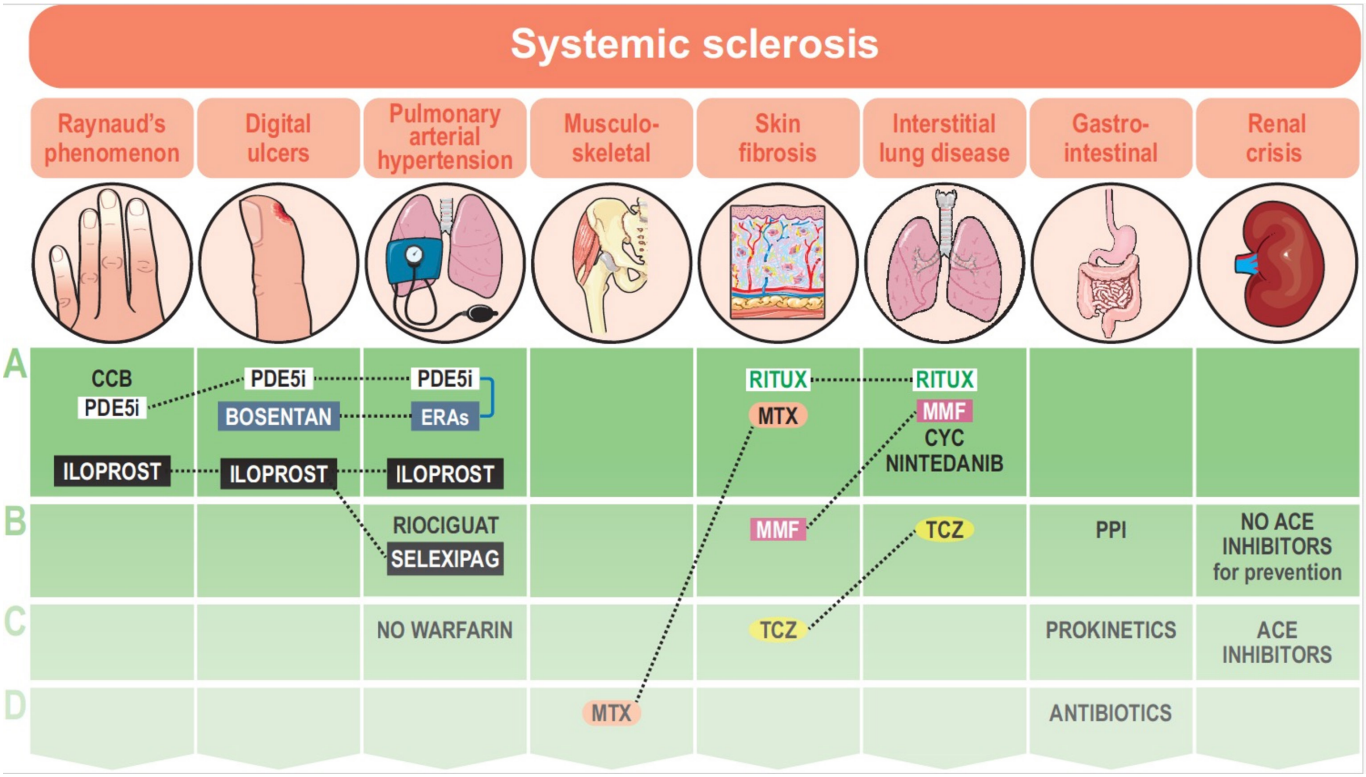

Figure 1 Schematic representation of the eight clinical domains covered by the 2023 recommendations. Note that severe prognosis is not represented. The different shades of green boxes labelled A–D represent the Strength of the Recommendation (SoR) as shown in the relative column of table 1. Dotted lines connect same drug or drug class across distinct clinical domains. CCB, calcium channel blocker; CYC, cyclophosphamide; ERAs, endothelin receptor antagonists; MMF, mycophenolate mofetil; MTX, methotrexate; PDE5i, phosphodiesterase five inhibitors; PPI, proton pump inhibitors; RITUX, rituximab; TCZ, tocilizumab.

disease, CTD and Non CTD) all in WHO functional class II or III, were randomised to ambrisentan 10 mg and tadalafil 40 mg in combination or the single intervention with placebo in a 2:1:1 ratio. The primary endpoint was time to first event of clinical failure (TtCF). Coghlan *et al* published a post hoc analysis on the 187 patients with CTD-PAH (103 on combination vs 84 on single intervention) and within this population on the 118 SSc-PAH patients (71 vs 47), adopting the same TtCF endpoint. The benefit of combination treatment was observed both in the CTD and SSc populations compared with monotherapy groups.[21]

Box 1 Research agenda

1. To evaluate the efficacy of immune suppression and/or other immune targeting DMARDs in the vascular and gastrointestinal manifestations of systemic sclerosis (SSc).
2. To evaluate the efficacy of non pharmacological interventions for the management of digital ulcers.
3. To evaluate the efficacy of biological interventions on cardiovascular manifestations of SSc.
4. To evaluate the efficacy of pharmacological and non pharmacological interventions in the management of calcinosis in SSc.
5. To evaluate the efficacy of new immunological interventions to expand the immune-suppression and antifibrotic portfolio and improve clinical outcome in SSc.
6. To evaluate the performance of a specific comprehensive patient-reported outcome for overall disease burden in SSc following patients' priorities.

Kuwana *et al* analysed a modified CTD and SSc-PAH intention-to-treat population, stratified by baseline characteristics and European Respiratory Society (ERS) risk at baseline (low/intermediate and high) using the TtCF at 16 weeks. In this analysis, risk of clinical failure was 53.7% lower in SSc-PAH treated with combination therapy. Details of study populations, endpoints and both analyses are in online supplemental extended results.[24–27]

The task force unanimously agreed to recommend the use of first-line combination treatment at diagnosis of PAH.

Intravenous epoprostenol should be considered for the treatment of SSc patients with advanced PAH (classes III and IV)

The task force agreed to retain this recommendation unchanged given the lack of any new study with higher LoE compared with previously.[7] The advanced/severe PAH indication is reflected in the graphic summary shown in figure 3.

Other prostacyclin analogues should be considered for the treatment of SSc PAH

Since the 2017 update, Gaine *et al* reported the results of a subanalysis of a phase 3 double-blind RCT for selexipag at maximum tolerated dose versus placebo in 1156 patients with PAH either on no treatment or on stable doses of PDE5i, ERAs or both.[28 29] The 170 patients with SSc-PAH (77 on treatment vs 93 on placebo) had a similar maximum tolerated dose despite slight difference in proportion of background therapy and showed an overall reduction in risk of a morbidity/mortality event of 44% (HR 0.56, 95 CI 0.34 to 0.91).[28] The task force considered the positive results of the subanalysis, although post hoc, and agreed to recommend the use of selexipag with SoR B (LoE 1b).

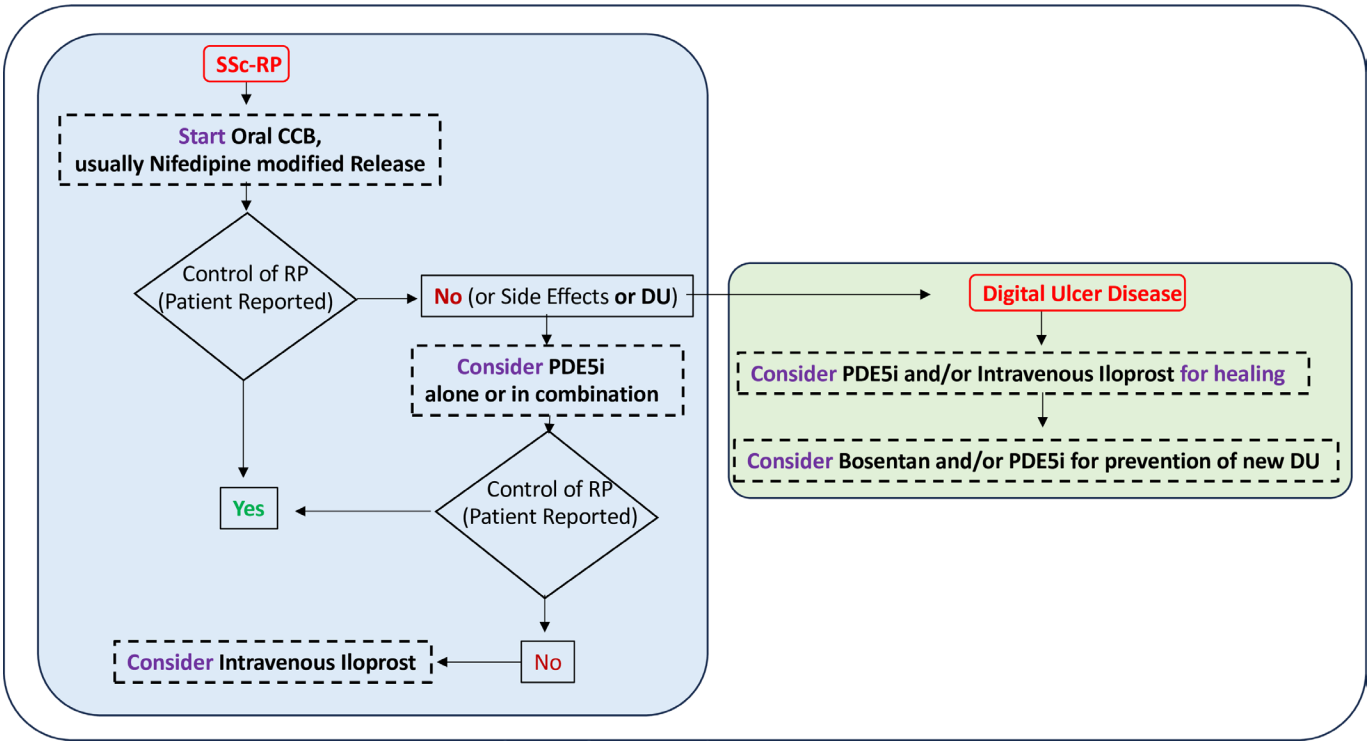

Figure 2 Treatment flow chart for the evidence informing the recommendation for treatment of SSc-related Raynaud's phenomenon (RP) and (ischaemic) DU disease. CCB, calcium channel blocker; DU, digital ulcer; PDE5i, phosphodiesterase 5 inhibitors; SSc, systemic sclerosis.

Riociguat can be considered for treatment of SSc-PAH

Humbert *et al* published the results of a post hoc analysis on SSc and CTD-PAH (PATENT-1) and its open-label, long-term extension (PATENT-2), evaluating the efficacy of riociguat 2.5 or 1.5 three times daily versus placebo on 6 min walk distance (6MWD), haemodynamics and WHO functional class.[30 31] The SSc-PAH population consisted of 66 patients, with 45 (68%) on background treatment including mainly ERAs.[31] SSc-PAH patients receiving riociguat reported a 4 min (±43) improvement in 6MWD at week 12 vs a 37 min (±120) worsening in the placebo group. This was associated with haemodynamic and WHO functional class improvement that persisted in the long-term analysis of PATENT-2. The results of this post hoc analysis were consistent with the results analysed in 2017 and this recommendation was left unchanged.[7]

The use of anticoagulants (warfarin) for the treatment of SSc-PAH is not recommended

Anticoagulants are widely used for the treatment of idiopathic PAH. Nevertheless, a meta-analysis of 4 CTD-PAH studies (3 prospective and 1 retrospective) including 392 patients with SSc, revealed that in SSc-PAH patients, there was a significant increase in mortality associated with the use of anticoagulants (HR 1.58 (95% CI 1.08 to 2.31); p=0.02),[32] although it noted an Australian observational study reported a benefit in 132 SSc-PAH patients including 37 receiving anticoagulants (for the indication of PAH in half). The task force, therefore, proposed to endorse a negative recommendation for the use of anticoagulants (mainly warfarin).[33]

Renal crisis

ACE inhibitors should be used immediately at diagnosis of SRC

Despite the absence of specific RCTs regarding the efficacy of ACE inhibitors (ACEi) on SRC, the task force commented on the substantial improvement in mortality rate observed since ACEi was implemented as a therapeutic option.[34] For this reason, the task force agreed with high LoA to maintain this recommendation substantially unchanged.[7]

It was noted that a meta-analysis of the literature evaluating the prognosis of SRC in SSc described a significantly poorer prognosis of SRC in patients with previous exposure to ACEi,[35] but a separate analysis of other factors that could have led to this poorer prognosis was not conducted. For this reason, the recommendation for the use of ACEi was not extended to a preventive recommendation. The task force also avoided formulating a negative recommendation on prevention both for the potential biases in the meta-analysis and to avoid the unintended consequence of reducing the use of ACE inhibitors. The Delphi exercise pre-SLR also prioritised the research question on the effectiveness of sartans on SRC outcome. The task force noted the lack of specific high-quality studies on this topic and did not formulate a recommendation. Nevertheless, it was discussed that the class may have a therapeutic effect similar to the ACEi and that studies on this topic are difficult to implement.

SSc patients treated with glucocorticoids should have regular monitoring of blood pressure to detect SRC

This recommendation is unchanged from 2017. The task force noted the heterogeneity of data in the literature on this topic, the lack of any higher level of evidence compared with 2017 and had high agreement in recommending regular monitoring of blood pressure when the use of glucocorticoids is deemed necessary and appropriate.

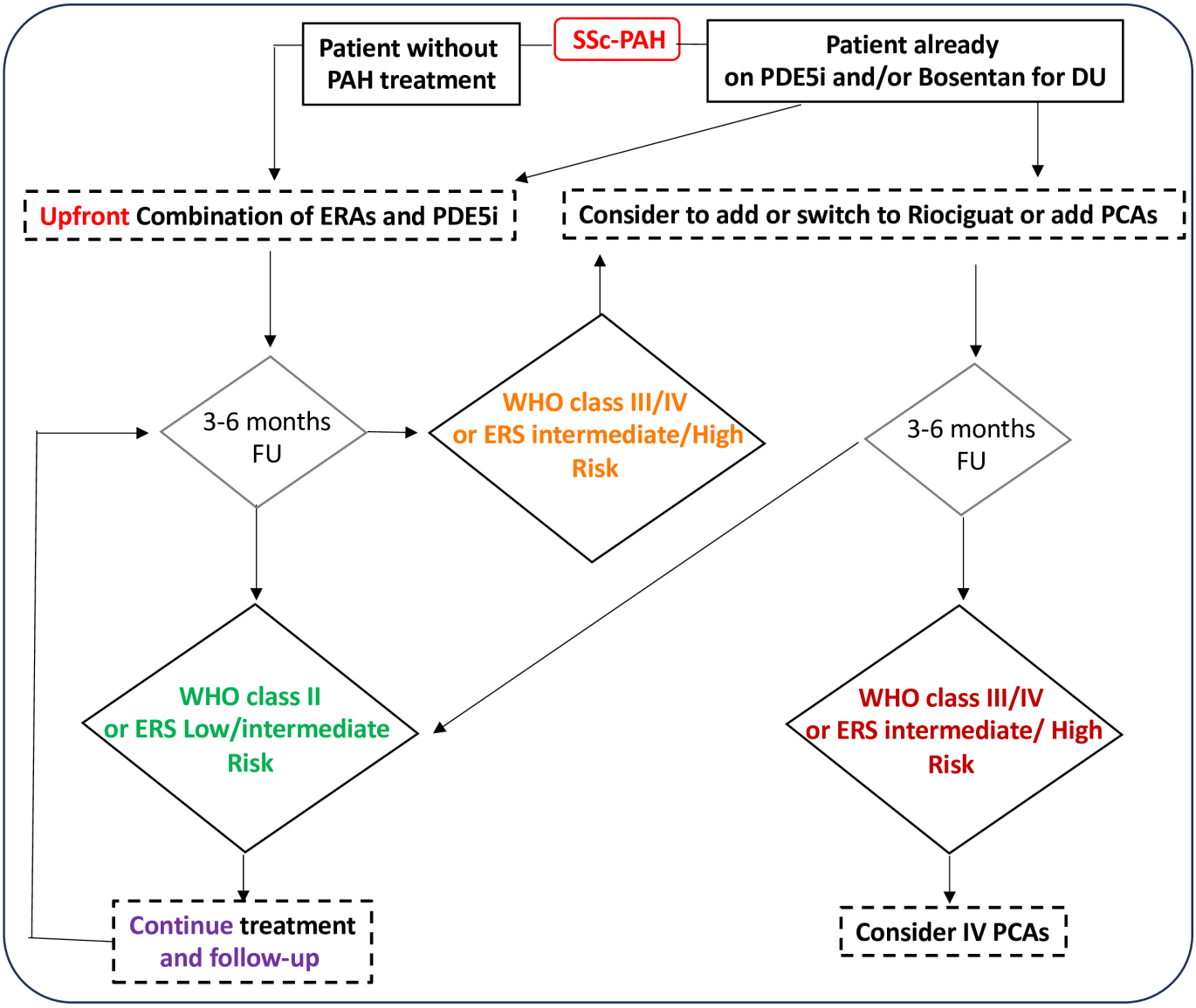

Figure 3 Treatment flow chart for the evidence informing the recommendations for treatment of SSc pulmonary artery hypertension (PAH). DU, digital ulcer; ERAs, endothelin receptor antagonists; ERS, European Respiratory Society; IV, intravenous; PCA, prostacyclin agonists.

GI involvement

Proton pump inhibitors should be considered for the treatment of SSc gastro-oesophageal reflux disease and prevention of oesophageal ulcers and strictures

The SLR found no specific studies demonstrating the beneficial effects of proton pump inhibitors (PPIs) on oesophageal involvement in SSc. Nevertheless, two independent cohort studies suggest that treatment with PPI may be only partially effective in controlling oesophagitis/gastritis[36] or abnormal oesophageal acid exposure.[37] The task force also commented on the lack of evidence on safety following long-term PPI use. The task force acknowledged the need to address gastro-oesophageal reflux disease with PPI treatment at least in first instance and recommended their use in an attempt to control symptoms and prevent oesophageal complications.

The use of prokinetic drugs should be considered for the treatment of symptomatic motility disturbances related to SSc

Since the 2017 updates, Foocharoen *et al* reported the results of an RCT involving 148 patients with SSc and partial response to high-dose PPI (omeprazole 20 mg two times per day).[38] Patients remained on PPI and were randomised to receive either domperidone or alginic acid (or matched placebos) for 4 weeks. Both groups had similar improvement in the severity of GERD symptoms, with 5 (13.2%) patients on domperidone and 8 (21.6%) on alginic acid who did not respond. In a smaller, open-label study, Karamanolis *et al* reported the positive effect of a single dose of buspirone (a 5-HT1A receptor agonist) in increasing lower oesophageal sphincter pressure compared with baseline and in comparison with domperidone.[39] Beyond oesophageal dysmotility, Vigone *et al* reported the effectiveness of prucalopride (a 5HT4 receptor agonist) as assessed by frequency of evacuations, UCLA GIT 2.0 constipation and Likert scales.[40–42]

The task force acknowledged the substantial unmet need for better control of GI manifestations in SSc.

The use of rotating antibiotics should be considered for the treatment of small intestinal bacterial overgrowth

The results of the SLR did not show any higher level of evidence compared with the 2017 update.[9] While acknowledging the

need for further studies, particularly addressing the specific effects of probiotics, the task force, with the strong support of patient representatives, retained the recommendation for the use of rotating antibiotics for the treatment of small intestinal bacterial overgrowth (SIBO) based on interventional studies using breath tests to confirm SIBO.[7 9]

Considering the sparse evidence on GI manifestations, and with the strong advocacy of patient representatives, the task force endorsed a high level of priority in the research agenda for GI disease in SSc (box 1). Future studies should span from the identification of treatments and interventions to achieve better symptom control to testing the efficacy of disease-modifying agents on the natural history of GI manifestations in SSc.

The immune suppression continuum across skin and lung fibrosis

Skin and lung fibrosis have been evaluated in many RCTs testing the efficacy of immune suppression and targeted treatments. This has led to major changes in recommendations compared with 2017.

Methotrexate, mycophenolate mofetil and/or rituximab should be considered for treatment of SSc skin fibrosis

There was no higher LoE on methotrexate (MTX) compared with the 2017 update. The main results informing this new recommendation derive from a randomised, double-blind, parallel-group trial that enrolled 142 patients with SSc-related ILD treated with mycophenolate mofetil (MMF) or oral cyclophosphamide (Scleroderma Lung Study (SLS) II).[43] Post hoc analyses of SLS-II identified modified Rodnan skin score (mRSS) improvements from baseline to 24 months for both MMF (–4.90, 95% CI −6.4 to −3.4) and cyclophosphamide (–5.35, 95% CI –6.9 to −3.8)).[43] Combined post hoc analyses of skin trajectories from the SLS-I trial (which compared cyclophosphamide to placebo and was included in the previous recommendations[44]) and the SLS-II trial[45] further confirmed the benefits of both mycophenolate mofetil (MMF) and cyclophosphamide in reducing skin fibrosis. The predominant adverse event was leucopenia that occurred in significantly more patients in the cyclophosphamide group than in the MMF group (30 vs 4 patients; $p<0.05$).

Further, one multicentre observational study including 326 early dcSSc patients showed no significant difference in mRSS across patients treated with MTX (n=65), MMF (n=118), cyclophosphamide (n=87) or no immunosuppressants[46] with a modest improvement in the mRSS in all groups at 12 months.

The strongest evidence for rituximab came from a double-blind RCT performed in Japan. In this study, 56 SSc patients were included with an mRSS of ≥10, and an expected survival of at least 6 months.[47] Patients received four intravenous doses of the assigned intervention (rituximab 375 mg/m^2 or placebo; once per week for 4 weeks). Notably, this is not the usual dose used for other rheumatic diseases. The absolute improvement in mRSS at 24 weeks was significantly higher in the rituximab group than in the placebo group (−6.30 vs 2.14; difference −8.44 (95% CI −11.00 to −5.88); $p<0.0001$). There was no difference in adverse events.

The task force considered the totality of the data (summarised in online supplemental extended results[47–49]) and recommended consideration of rituximab for the treatment of skin fibrosis in SSc.

Tocilizumab may be considered for the treatment of skin fibrosis in patients with early, inflammatory dcSSc

Tocilizumab has been investigated in a clinical development programme where skin disease was the primary outcome measure and target population enriched for early, inflammatory disease. In a phase 2 trial, the target population included DcSSc patients with mRSS>15.[50] 87 patients were enrolled, and the least squares mean (LSM) change in mRSS at 48 weeks was −6.33 in the tocilizumab group and −2.77 in the placebo group (treatment difference −3.55, 95% CI −7.23 to 0.12; $p=0.0579$). In a phase 3 trial of 210 patients, which included patients with mRSS>10,[51] there was an LSM change in mRSS from baseline to week 48 of −6.14 for tocilizumab and −4.41 for placebo (adjusted difference −1.73 (95% CI −3.78 to 0.32); $p=0.10$). Detailed results are summarised in online supplemental extended results. Although these data do not support the use of tocilizumab as first-line therapy for skin involvement in early dcSSc,[52] a trend in benefit was observed together with a satisfactory safety profile, so the task force agreed to considering tocilizumab for the treatment of skin fibrosis in patients with early, inflammatory dcSSc.

Only one randomised, double-blind, placebo-controlled trial has been performed (in Japan) with intravenous immunoglobulin (IVIG) versus placebo in 63 DcSSc patients (see online supplemental extended results).[53] No changes in the mRSS were observed at 24 weeks but the mRSS at 60 weeks after the first administration was significantly reduced in patients with at least two courses of IVIG versus the group treated with a single course ($p=0.0040$). The task force agreed that additional studies are required to clarify the potential efficacy of IVIG in SSc skin involvement.

Mycophenolate mofetil, cyclophosphamide or rituximab should be considered for the treatment of SSc-ILD

The SLS II compared a continuous 24-month course of MMF to a 12-month course of oral cyclophosphamide (followed by 12 months of placebo) in an RCT of SSc-ILD patients (see Tashkin *et al*[43] and online supplemental extended results). Each treatment group showed significant improvement in % predicted FVC at 24 months, 2.19% (95% CI 0.53% to 3.84%) for the MMF group and 2.88% (95% CI 1.19% to 4.58%) for the cyclophosphamide group. MMF was better tolerated than cyclophosphamide based on the time to patient withdrawal, the number of treatment failures and incidence of leucopoenia and thrombocytopaenia. The task force noted that the SLS studies[43 44] investigated oral cyclophosphamide and there were insufficient data to compare the risk/benefit ratio of oral versus intravenous route for the treatment of SSc-ILD.

Based on these and other consistent data (online supplemental extended results)[43 44 54], the task force agreed to recommend both MMF and cyclophosphamide for the treatment of SSc-ILD (A).

The RECITAL trial compared rituximab to intravenous cyclophosphamide in a basket design including ILD related to 3 CTDs (97 patients including 37 with SSc) (see online supplemental extended results).[55] At week 24, both groups showed improvement with unadjusted mean gain from baseline in FVC of 99 mL (SD 329; relative change 4.35% (SD 15.67)) in the cyclophosphamide group and 97 mL (234; 4.31% (11.80)) in the rituximab group. More adverse events were reported in the cyclophosphamide group (646 events) than in the rituximab group (445 events). Further, in the phase 2 DESIRES clinical trial (see online supplemental extended results[47]), the predicted

FVC at 24 weeks compared with baseline was significantly improved in the rituximab group compared with the placebo group (0.09% vs –2.87%; difference 2.96% (95% CI 0.08% to 5.84%); p=0.044).

Open-label studies and meta-analysis of 20 studies further supported the beneficial effects of rituximab on FVC in SSc-ILD (see online supplemental extended results)[56 57], therefore the task force recommended that rituximab should be considered for the treatment of SSc-ILD.

Nintedanib should be considered alone or in combination with MMF for the treatment of SSc ILD

Since the last update of the recommendations, the largest clinical trial ever conducted in SSc investigated the effects of the tyrosine-kinase inhibitor nintedanib in SSC ILD, SENSCIS (see online supplemental extended results).[58 59] While several other tyrosine kinase inhibitors have been tested in proof-of-concept studies, no other molecule has been ever evaluated as a disease-modifying agent for SSc or SSc-ILD in a large international multicentre phase III trial. In SENSCIS, 576 SSc-ILD patients were randomly assigned to receive 150 mg of nintedanib, administered orally twice daily or placebo. In the primary endpoint analysis, the adjusted annual rate of change in FVC was −52.4 mL per year in the nintedanib group and −93.3 mL per year in the placebo group (p=0.04). Other prespecified endpoints were not met, and adverse events were higher in the nintedanib group (16.0% vs 8.7%). Diarrhoea, the most common adverse event, was reported in 75.7% of the patients in the nintedanib group (vs 31.6% in the placebo group). The 52 weeks open-label extension study (SENSICS-ON) confirmed the similar changes in FVC and the safety profile seen in SENSCIS.[60]

Importantly, patients included in the SENSCIS trial were stratified for the use of MMF and preplanned subanalysis included evaluation of the primary endpoint by MMF use.[61] The relative treatment effect of nintedanib was similar (40% for those taking MMF at baseline and 46% for those not using) and consistent with that observed in the overall population (44%). The treatment effect of nintedanib on the annual rate of FVC decline was numerically greater in participants who were not taking MMF at baseline (difference: 55.4 mL per year (95% CI 2.3 to 108.5)) than in those who were taking MMF (26.3 mL per year (–27.9 to 80.6). The adverse event profile of nintedanib was generally similar with or without MMF.

Very importantly, the INBUILD trial further assessed nintedanib in a basket population of progressive fibrosing ILD (PF-ILD). In this phase 3 trial, patients were assigned to receive nintedanib (150 mg two times per day) or placebo while background immunosuppressants at inclusion were not allowed.[62] It is important to note that the inclusion criteria of INBUILD built the foundation for the definition of PF-ILD, formally only agreed on consensus in 2020.[63] Among 170 patients with autoimmune disease-related ILDs (including 39 SSc-ILD), the rate of decline in FVC over 52 weeks was −75.9 mL/year with nintedanib vs −178.6 mL/year with placebo (difference 102.7 mL/year (95% CI 23.2 to 182.2); nominal p=0.012).

Considering the results of the SENSCIS and INBUILD trials and the results concerning those concomitantly treated with mycophenolate, the task force recommended that nintedanib should be considered alone or in combination with MMF for the treatment of SSc ILD (A)

Tocilizumab should be considered for the treatment of SSc-ILD

Within the two trials having mRSS as primary endpoint discussed above, changes in FVC were assessed as secondary endpoint (see online supplemental extended results).[50–52] The 24-week study clearly showed significantly smaller decrease in FVC for tocilizumab than for placebo (tocilizumab –34 mL vs placebo –171 mL; p=0.0368).[50] In the phase 3 trial, the 48-week LSM change from baseline in FVC% predicted was –4.6 in the placebo group and –0.4 in the tocilizumab group (difference 4.2 (95% CI 2.0 to 6.4); nominal p=0.0002).[51] Based on these data, the FDA approved the use of tocilizumab for the treatment of SSc-ILD. The task force acknowledged that ILD was not the primary objective of both these tocilizumab trials, although it was prespecified as secondary outcome in the phase 3 trial. As well, the magnitude of effect between the two arms was large although the drug was investigated with no background treatment in an early, inflammatory population. As a result of discussion, the task force agreed to recommend that tocilizumab should be considered for the treatment of SSc-ILD. A diagram summarising different options for SSc-ILD treatment is shown in figure 4.

High-intensity immunosuppression in patients with poor prognosis

High-intensity immunosuppression (usually including cyclophosphamide) followed by autologous haematopoietic stem cell transplantation (HSCT) may be considered for the treatment of selected patients with early severe dcSSc and poor prognosis, in the absence of advanced cardiorespiratory involvement.

This recommendation is essentially unchanged since the 2017 update.[7] Since the previous literature review, the SCOT study (Scleroderma Cyclophosphamide or Transplantation) reported the 54 months beneficial effect of autologous HSCT on a combined morbidity/mortality outcome (see online supplemental extended results).[64] Patients were randomised 1:1 to receive either cyclophosphamide (500–750 mg/m^2) for 12 months or high-dose cyclophosphamide (120 mg/kg) together with equine anti-thymocyte globulin and total body irradiation, preceded by bone marrow mobilisation and leukapheresis and followed by auto transplant of haematopoietic stem cells (median 5.6 million CD34+cells/kg). The study endpoint was the Global Ranked Composite Score (see online supplemental extended results[65 66]), which favoured 67% of patients in the transplant arm vs 33% in the cyclophosphamide arm (p=0.01). The event-free survival analysis showed accordingly, that 74% of patients in the transplant arm remained event free at month 72 vs 47% of patients in the cyclophosphamide arm. The task force acknowledged that HSCT was never compared with other means of immunosuppression or targeted therapies and that treatment-related mortality needs to be carefully considered, especially in patients with suboptimal cardiac function, but the unambiguous efficacy of the intervention informed this recommendation.

Musculoskeletal involvement

MTX should be considered for the treatment of musculoskeletal involvement in SSc

This recommendation is unchanged from 2017. Although musculoskeletal involvement is common, and highly ranked by patients as a major concern with respect to disease burden, the SLR revealed a lack of good quality evidence for the impact of corticosteroids, tocilizumab or rituximab on joint involvement.[9]

Some case series suggested some effectiveness of abatacept on joint involvement but, in a phase 2 trial, there were no

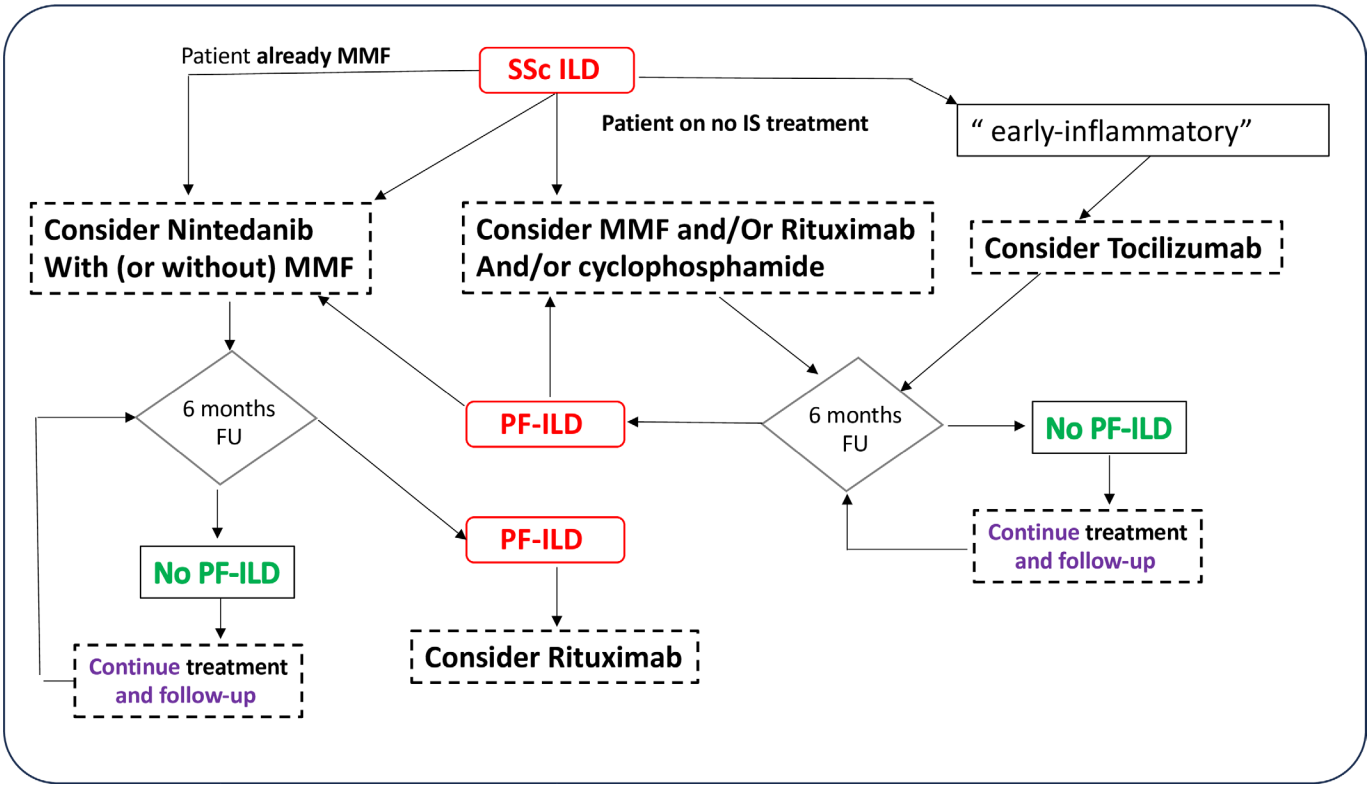

Figure 4 Treatment flow chart the evidence informing the recommendations for treatment of SSc interstitial lung disease (ILD). ILD, interstitial lung disease; IS, immune suppressive; MMF, mycophenolate mofetil; PF, progressive fibrosing; SSc, systemic sclerosis.

significant differences between the abatacept and placebo groups at 12 months in the swollen and tender joint counts, although significant and clinically meaningful treatment differences were observed in the HAQ DI.[67 68]

In a study of very small sample size and atypical trial design, IVIG seemed to slightly improve joint outcomes, but more data are required.[69]

There was also a lack of evidence for benefit of musculoskeletal involvement for JAK inhibitors despite some case reports, and the single randomised trial that investigated tofacitinib did not show benefit on joints.[70]

Research agenda and discussion

During the NGT discussions, specific aspects of SSc management were highlighted as a priority for research agenda, either due to the lack of current evidence and/or for the unmet need advocated by experts and patient representatives. These items are summarised in box 1.

The increase in a number of current recommendations (increased from 16 in 2017) reflects the increased knowledge across the eight clinical domains and, most importantly, newly available therapies. A 'one-size-fits-all' strategy cannot be implemented in SSc where disease duration, comorbidities, patient preferences, local availability and cost of medication should all be considered for informed decision-making.

The big advances made in SSc vasculopathy management emphasise the treatment continuum for the use of various vasodilators and anti-remodelling drugs from Raynaud's to DU and pulmonary arterial hypertension. Similarly, a therapeutic continuum in the interventions for skin and lung fibrosis is also apparent. These latter two domains are the ones with the most important updated information, resulting in recommendations for the use of MMF and/or rituximab, and tocilizumab for both skin and lung and nintedanib to be used alone or in combination with MMF for the treatment of SSc-ILD. While the inclusion criteria of the related trials enabled the task force to derive preliminary flow charts for the treatment of SSc-ILD (which need to be interpreted in line with the main recommendations), dedicated trials to test potential synergistic combinations (including with antifibrotic agents), or the early implementation of immune targeted approaches, are needed. Given the difficulty in implementing combination trials, high-quality real-world data may contribute to build evidence in this direction in the future.

Cell therapy has long been investigated in fibrotic diseases. In SSc, immunosuppression followed by HSCT may be considered for the treatment of selected patients with early dcSSc and poor prognosis . Although comparative trials may never occur, some observational data raised the effectiveness of combination therapy including rituximab as an alternative for these poor prognosis patients.[71] Furthermore, the availability of CAR-T cells and the first experience with CD19 CAR T cells in autoimmune disease is poised to disrupt the field.[72 73]

During the NGTs, the task force agreed on the importance of the patient's view in guiding future research. While some progress has been made with large studies and the development of new outcome measures (SCLERO-ID),[74] patient representatives strongly advocated the need for high-level evidence in the management of GI and musculoskeletal manifestations, which are consequently prioritised in the current research agenda (box 1).

In conclusion, the 2023 update of the EULAR recommendations for the management of SSc provides state-of-the-art guidance for physicians globally.

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Correction notice This article has been corrected since it published Online First. Affiliation 8 has been added.

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REFERENCES

1 Volkmann ER, Andréasson K, Smith V. Systemic sclerosis. *Lancet* 2023;401:304–18.
2 Denton CP, Khanna D. Systemic sclerosis. *The Lancet* 2017;390:1685–99.
3 Del Galdo F, Hartley C, Allanore Y. Randomised controlled trials in systemic sclerosis: patient selection and endpoints for next generation trials. *Lancet Rheumatol* 2020;2:e173–84.
4 Lescoat A, Huang S, Carreira PE, *et al*. Cutaneous Manifestations, Clinical Characteristics, and Prognosis of Patients With Systemic Sclerosis Sine Scleroderma: Data From the International EUSTAR Database. *JAMA Dermatol* 2023;159:837–47.
5 Parodis I, Girard-Guyonvarc'h C, Arnaud L, *et al*. EULAR recommendations for the non-pharmacological management of systemic lupus erythematosus and systemic sclerosis. *Ann Rheum Dis* 2023.
6 Kowal-Bielecka O, Landewé R, Avouac J, *et al*. EULAR recommendations for the treatment of systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group (EUSTAR). *Ann Rheum Dis* 2009;68:620–8.
7 Kowal-Bielecka O, Fransen J, Avouac J, *et al*. Update of EULAR recommendations for the treatment of systemic sclerosis. *Ann Rheum Dis* 2017;76:1327–39.
8 van der Heijde D, Aletaha D, Carmona L, *et al*. 2014 Update of the EULAR standardised operating procedures for EULAR-endorsed recommendations. *Ann Rheum Dis* 2015;74:8–13.
9 Lescoat A, Bertoldo E, Colic J, *et al*. POS1260 SYSTEMATIC literature review for the 2023 update of eular recommendations for the treatment of systemic sclerosis. *Ann Rheum Dis* 2023;82:973.
10 OCEBM levels of evidence — centre for evidence-based medicine (cebm). University of Oxford; 2023. Available: https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebm-levels-of-evidence [Accessed 6 Jun 2023].
11 Guyatt G, Oxman AD, Akl EA, *et al*. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;64:383–94.
12 Allanore Y, Distler O, Matucci-Cerinic M, *et al*. Review: Defining a Unified Vascular Phenotype in Systemic Sclerosis. *Arthritis Rheumatol* 2018;70:162–70.
13 Roustit M, Blaise S, Allanore Y, *et al*. Phosphodiesterase-5 inhibitors for the treatment of secondary Raynaud's phenomenon: systematic review and meta-analysis of randomised trials. *Ann Rheum Dis* 2013;72:1696–9.
14 Hachulla E, Hatron P-Y, Carpentier 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.
15 Rosato E, Molinaro I, Borghese F, *et al*. Bosentan improves skin perfusion of hands in patients with systemic sclerosis with pulmonary arterial hypertension. *J Rheumatol* 2010;37:2531–9.
16 Bose N, Bena J, Chatterjee S. Evaluation of the effect of ambrisentan on digital microvascular flow in patients with systemic sclerosis using laser Doppler perfusion imaging: a 12-week randomized double-blind placebo controlled trial. *Arthritis Res Ther* 2015;17:44.
17 Khanna D, Denton CP, Merkel PA, *et al*. Effect of Macitentan on the Development of New Ischemic Digital Ulcers in Patients With Systemic Sclerosis: DUAL-1 and DUAL-2 Randomized Clinical Trials. *JAMA* 2016;315:1975–88.

18 Seibold JR, Wigley FM, Schiopu E, *et al*. Digital Ulcers in Ssc Treated with Oral Treprostinil: A Randomized, Double-Blind, Placebo-Controlled Study with Open-Label Follow-up. *J Scleroderma Relat Disord* 2017;2:42–9.
19 Agarwal V, Ghosh P, Sharma A, *et al*. ACR ANNUAL SCIENTIFIC MEETING Abstract #2086: Efficacy of Tadalafil in Raynaud's Phenomenon Secondary to Systemic Sclerosis: A Double Blind Randomized Placebo Controlled Parallel Group Multicentric Study. *Arthritis Rheum* 2010;62:S872.
20 Tingey T, Shu J, Smuczek J, *et al*. Meta-analysis of healing and prevention of digital ulcers in systemic sclerosis. *Arthritis Care Res (Hoboken)* 2013;65:1460–71.
21 Galiè N, Barberà JA, Frost AE, *et al*. Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension. *N Engl J Med* 2015;373:834–44.
22 Coghlan JG, Galiè N, Barberà JA, *et al*. Initial combination therapy with ambrisentan and tadalafil in connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH): subgroup analysis from the AMBITION trial. *Ann Rheum Dis* 2017;76:1219–27.
23 Kuwana M, Blair C, Takahashi T, *et al*. Initial combination therapy of ambrisentan and tadalafil in connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH) in the modified intention-to-treat population of the AMBITION study: post hoc analysis. *Ann Rheum Dis* 2020;79:626–34.
24 Hassoun PM, Zamanian RT, Damico R, *et al*. Ambrisentan and Tadalafil Up-front Combination Therapy in Scleroderma-associated Pulmonary Arterial Hypertension. *Am J Respir Crit Care Med* 2015;192:1102–10.
25 Pestaña-Fernández M, Rubio-Rivas M, Tolosa-Vilella C, *et al*. Longterm Efficacy and Safety of Monotherapy versus Combination Therapy in Systemic Sclerosis-associated Pulmonary Arterial Hypertension: A Retrospective RESCLE Registry Study. *J Rheumatol* 2020;47:89–98.
26 Lammi MR, Mathai SC, Saketkoo LA, *et al*. Association Between Initial Oral Therapy and Outcomes in Systemic Sclerosis-Related Pulmonary Arterial Hypertension. *Arthritis Rheumatol* 2016;68:740–8.
27 Lei Y, Zhang X, Lin H, *et al*. The effects of oral treatment for systemic sclerosis related pulmonary arterial hypertension: A systematic review and meta-analysis. *Mod Rheumatol* 2021;31:151–61.
28 Gaine S, Chin K, Coghlan G, *et al*. Selexipag for the treatment of connective tissue disease-associated pulmonary arterial hypertension. *Eur Respir J* 2017;50:1602493.
29 Sitbon O, Channick R, Chin KM, *et al*. Selexipag for the Treatment of Pulmonary Arterial Hypertension. *N Engl J Med* 2015;373:2522–33.
30 Ghofrani H-A, Galiè N, Grimminger F, *et al*. Riociguat for the treatment of pulmonary arterial hypertension. *N Engl J Med* 2013;369:330–40.
31 Humbert M, Coghlan JG, Ghofrani H-A, *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.
32 Khan MS, Usman MS, Siddiqi TJ, *et al*. Is Anticoagulation Beneficial in Pulmonary Arterial Hypertension? *Circ Cardiovasc Qual Outcomes* 2018;11:e004757.
33 Morrisroe K, Stevens W, Huq M, *et al*. Survival and quality of life in incident systemic sclerosis-related pulmonary arterial hypertension. *Arthritis Res Ther* 2017;19:122.
34 Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972-2002. *Ann Rheum Dis* 2007;66:940–4.
35 Xiong A, Cao Y, Xiang Q, *et al*. Angiotensin-converting enzyme inhibitors prior to scleroderma renal crisis in systemic sclerosis: A systematic review and meta-analysis. *J Clin Pharm Ther* 2022;47:722–31.
36 Petcu A, Ghib LJ, Grad SM, *et al*. Upper gastrointestinal involvement in systemic sclerosis: Findings in a real-life setting. *Exp Ther Med* 2019;18:5095–100.
37 Stern EK, Carlson DA, Falmagne S, *et al*. Abnormal esophageal acid exposure on high-dose proton pump inhibitor therapy is common in systemic sclerosis patients. *Neurogastroenterol Motil* 2018;30.
38 Foocharoen C, Chunlertrith K, Mairiang P, *et al*. Effectiveness of add-on therapy with domperidone vs alginic acid in proton pump inhibitor partial response gastro-oesophageal reflux disease in systemic sclerosis: randomized placebo-controlled trial. *Rheumatology (Oxford)* 2017;56:214–22.
39 Karamanolis GP, Panopoulos S, Karlaftis A, *et al*. Beneficial effect of the 5-HT1A receptor agonist buspirone on esophageal dysfunction associated with systemic sclerosis: A pilot study. *United European Gastroenterol J* 2015;3:266–71.
40 Vigone B, Caronni M, Severino A, *et al*. Preliminary safety and efficacy profile of prucalopride in the treatment of systemic sclerosis (SSc)-related intestinal involvement: results from the open label cross-over PROGASS study. *Arthritis Res Ther* 2017;19:145.
41 Zampatti N, Garaiman A, Jordan S, *et al*. Performance of the UCLA Scleroderma Clinical Trials Consortium Gastrointestinal Tract 2.0 instrument as a clinical decision aid in the routine clinical care of patients with systemic sclerosis. *Arthritis Res Ther* 2021;23:125.
42 Khanna D, Furst DE, Maranian P, *et al*. Minimally important differences of the UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument. *J Rheumatol* 2011;38:1920–4.
43 Tashkin DP, Roth MD, Clements PJ, *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.
44 Tashkin DP, Elashoff R, Clements PJ, *et al*. Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med* 2006;354:2655–66.
45 Namas R, Tashkin DP, Furst DE, *et al*. Efficacy of Mycophenolate Mofetil and Oral Cyclophosphamide on Skin Thickness: Post Hoc Analyses From Two Randomized Placebo-Controlled Trials. *Arthritis Care Res (Hoboken)* 2018;70:439–44.
46 Herrick AL, Pan X, Peytrignet S, *et al*. Treatment outcome in early diffuse cutaneous systemic sclerosis: the European Scleroderma Observational Study (ESOS). *Ann Rheum Dis* 2017;76:1207–18.
47 Ebata S, Yoshizaki A, Oba K, *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.
48 Boonstra M, Meijs J, Dorjée AL, *et al*. Rituximab in early systemic sclerosis. *RMD Open* 2017;3:e000384.
49 Moradzadeh M, Aghaei M, Mehrbakhsh Z, *et al*. Efficacy and safety of rituximab therapy in patients with systemic sclerosis disease (SSc): systematic review and meta-analysis. *Clin Rheumatol* 2021;40:3897–918.
50 Khanna D, Denton CP, Jahreis A, *et al*. Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomised, controlled trial. *Lancet* 2016;387:2630–40.
51 Khanna D, Lin CJF, Furst DE, *et al*. Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med* 2020;8:963–74.
52 Khanna D, Lin CJF, Furst DE, *et al*. Long-Term Safety and Efficacy of Tocilizumab in Early Systemic Sclerosis-Interstitial Lung Disease: Open-Label Extension of a Phase 3 Randomized Controlled Trial. *Am J Respir Crit Care Med* 2022;205:674–84.
53 Takehara K, Ihn H, Sato S. A randomized, double-blind, placebo-controlled trial: intravenous immunoglobulin treatment in patients with diffuse cutaneous systemic sclerosis. *Clin Exp Rheumatol* 2013;31:151–6.
54 Volkmann ER, Tashkin DP, Li N, *et al*. Mycophenolate Mofetil Versus Placebo for Systemic Sclerosis-Related Interstitial Lung Disease: An Analysis of Scleroderma Lung Studies I and II. *Arthritis Rheumatol* 2017;69:1451–60.
55 Maher TM, Tudor VA, Saunders P, *et al*. Rituximab versus intravenous cyclophosphamide in patients with connective tissue disease-associated interstitial lung disease in the UK (RECITAL): a double-blind, double-dummy, randomised, controlled, phase 2b trial. *Lancet Respir Med* 2023;11:45–54.
56 Sircar G, Goswami RP, Sircar D, *et al*. Intravenous cyclophosphamide vs rituximab for the treatment of early diffuse scleroderma lung disease: open label, randomized, controlled trial. *Rheumatology (Oxford)* 2018;57:2106–13.
57 Goswami RP, Ray A, Chatterjee M, *et al*. Rituximab in the treatment of systemic sclerosis-related interstitial lung disease: a systematic review and meta-analysis. *Rheumatology (Oxford)* 2021;60:557–67.
58 Distler O, Highland KB, Gahlemann M, *et al*. Nintedanib for Systemic Sclerosis-Associated Interstitial Lung Disease. *N Engl J Med* 2019;380:2518–28.
59 Khanna D, Maher TM, Volkmann ER, *et al*. Effect of nintedanib in patients with systemic sclerosis-associated interstitial lung disease and risk factors for rapid progression. *RMD Open* 2023;9:e002859.
60 Allanore Y, Vonk MC, Distler O, *et al*. Continued treatment with nintedanib in patients with systemic sclerosis-associated interstitial lung disease: data from SENSCIS-ON. *Ann Rheum Dis* 2022;81:1722–9.
61 Highland KB, Distler O, Kuwana M, *et al*. Efficacy and safety of nintedanib in patients with systemic sclerosis-associated interstitial lung disease treated with mycophenolate: a subgroup analysis of the SENSCIS trial. *Lancet Respir Med* 2021;9:96–106.
62 Flaherty KR, Wells AU, Cottin V, *et al*. Nintedanib in Progressive Fibrosing Interstitial Lung Diseases. *N Engl J Med* 2019;381:1718–27.
63 George PM, Spagnolo P, Kreuter M, *et al*. Progressive fibrosing interstitial lung disease: clinical uncertainties, consensus recommendations, and research priorities. *Lancet Respir Med* 2020;8:925–34.
64 Sullivan KM, Goldmuntz EA, Keyes-Elstein L, *et al*. Myeloablative Autologous Stem-Cell Transplantation for Severe Scleroderma. *N Engl J Med* 2018;378:35–47.
65 Ait Abdallah N, Wang M, Lansiaux P, *et al*. Long term outcomes of the French ASTIS systemic sclerosis cohort using the global rank composite score. *Bone Marrow Transplant* 2021;56:2259–67.
66 van Laar JM, Farge D, Sont JK, *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.
67 Castellví I, Elhai M, Bruni C, *et al*. Safety and effectiveness of abatacept in systemic sclerosis: The EUSTAR experience. *Semin Arthritis Rheum* 2020;50:1489–93.
68 Khanna D, Spino C, Johnson S, *et al*. Abatacept in Early Diffuse Cutaneous Systemic Sclerosis: Results of a Phase II Investigator-Initiated, Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial . *Arthritis & Rheumatology* 2020;72:125–36.
69 Nacci F, Righi A, Conforti ML, *et al*. Intravenous immunoglobulins improve the function and ameliorate joint involvement in systemic sclerosis: a pilot study. *Ann Rheum Dis* 2007;66:977–9.
70 Khanna D, Padilla C, Tsoi LC, *et al*. Tofacitinib blocks IFN-regulated biomarker genes in skin fibroblasts and keratinocytes in a systemic sclerosis trial. *JCI Insight* 2022;7:e159566.

71 Keret S, Henig I, Zuckerman T, *et al*. Outcomes in progressive systemic sclerosis treated with autologous hematopoietic stem cell transplantation compared with combination therapy. *Rheumatology (Oxford)* 2024;63:1534–8.
72 Bergmann C, Müller F, Distler JHW, *et al*. Treatment of a patient with severe systemic sclerosis (SSc) using CD19-targeted CAR T cells. *Ann Rheum Dis* 2023;82:1117–20.
73 Merkt W, Freitag M, Claus M, *et al*. Third-generation CD19.CAR-T cell-containing combination therapy in Scl70+ systemic sclerosis. *Ann Rheum Dis* 2024;83:543–6.
74 Becker MO, Dobrota R, Garaiman A, *et al*. Development and validation of a patient-reported outcome measure for systemic sclerosis: the EULAR Systemic Sclerosis Impact of Disease (ScleroID) questionnaire. *Ann Rheum Dis* 2022;81:507–15.

Supplementary file 1
Extended results

PDE-5 inhibitors should also be considered for treatment of SSc-RP (A) (1a).

Since previous set of recommendations, a meta-analysis of six RCTs published between 2005 and 2012 was conducted by Roustit et al.[13]. The 6 RCTs included 224 patients (95% of whom were classifiable as SSc), adopted different double-blind designs (parallel or cross-over) and distinct interventions (sildenafil 50mg/bd, sildenafil modified release up to 200mg/day, tadalafil up to 20mg/daily and Vardenafil 10 mg/bd). RCTs were all blinded and all against placebo. The metanalysis considered the effect of the class (Phosphodiesterase-5 inhibitors (PDE-5i), despite differences in molecule, dose and trial design. PDE-5 inhibitors pooled as intervention group, showed an overall improvement of Raynaud's condition score against placebo [mean difference -0.46 (95% CI -0.74 to -0.147); p=0.002]. Significant differences were also noted on daily frequency of RP attacks [mean difference -0.49 (95% CI -0.71 to -0.28; p<0.0001] and daily duration of RP attacks in minutes [-14.62 (-20.25 to -9); p<0.0001]. Treatment effect was altogether moderate, although statistically significant and safety was not addressed. One new RCT evaluating the efficacy of sildenafil (60mg/day) vs placebo in 84 patients with SSc and at least one active DU did not support the use of sildenafil for RP, but RP was only a secondary outcome measure in this study that was negative for its primary objective that evaluated time to DU healing as primary outcome[14]. Therefore, the high level of evidence provided by the 2013 meta-analysis still supported previous recommendations for the use of PDE-5i on SSc-RP[13].

One non-randomised controlled trial included in the previous set of recommendations showed no additional benefit of Bosentan over CCB for the treatment of RP as assessed with the Raynaud's condition score (RCS)[15]. On the contrary Bose et al reported the effectiveness of increasing doses of Ambrisentan over 12 weeks on RCS as secondary endpoint in a 3:1 randomisation vs placebo in a small patient population (N=20)[16]. Ambrisentan was associated with numerical improvement in microvascular flow, as assessed by laser doppler perfusion, and a marginal but significant improvement in RCS at week 12. In the negative DUAL 1 and 2 trials assessing the efficacy of Macitentan on the development of new digital ulcers (DU), activity limitation due to RP was explored as secondary outcome and did not differentiate active therapy from placebo in both trials[17]. Given this contradicting and relatively weak new set of evidence, the task force unanimously agreed not to formulate any recommendation for or against the use of ERA in RP.

PDE-5 inhibitors (1a) and/or intravenous iloprost (1a) should be considered for the treatment of digital ulcers in patients with SSc (A).

The SLR did not identify any new study on the effect of intravenous Iloprost for the healing of DU with higher level of evidence compared to the 2017 recommendations[7].

On the contrary, one RCT failed to demonstrate efficacy of oral treprostinil in DU healing and prevention[18]. Specifically, oral treprostinil was tested in a Randomized, Double-Blind, placebo-controlled study on 148 patients with SSc, all having at least one DU deemed "active" per protocol definition. The mean net ulcer burden at 20 weeks was not significantly different in the 71 treated subjects vs the 76 on placebo[18]. On review of this evidence, the task force agreed to maintain the recommendations limited to intravenous iloprost for treatment of DU, based on previous studies.

As for the use of PDE-5i, the there was no strongest evidence compared to the SEDUCE study, already evaluated in the previous update (7) , hence the task force agreed to maintain the previous recommendations, to consider the use of PDE-5i for the healing of DU (A) (1a).

On discussion of the SEDUCE study, the task force commented on the particularly high rate of DU healing, putatively associated with effective local treatment in highly experienced centers,

which was not recorded/accounted or corrected for, in the analysis. This latter consideration contributed to inform the research agenda on this important clinical manifestation of SSc, described in more detail below (**Box 1**).

A second RCT, primarily focused on the effect of tadalafil on RP but only published as abstract (abstract#2086 from [19]), also reported as secondary endpoint a significant effect in rate of healing of DU in patients with SSc-RP)[13,19]. A metanalysis of 3 RCTs investigating PDE-5i in RP (already analysed in 2017 recommendations) showed a pooled effect of significant benefit on DU healing, both in the number of patients with DUs healing and the number of patients with DUs [7,20].

In view of these considerations, the task force unanimously agreed to maintain the previous recommendations

Bosentan should be considered for reduction of number of new Digital Ulcers in SSc (A) (1a).

This recommendation is unchanged from 2017 since no new or higher-level evidence has been identified for the use of Bosentan in DU [7]. It is to be noted that the recommendation remains specifically for bosentan instead of being extended to the ERA class given the negative results of two RCTs evaluating the efficacy of macitentan in more than 400 patients with SSc DU. Specifically, DUAL-1 and DUAL2 studies found no significant difference across patients treated with macitentan 3mg/day, macitentan 10mg/day or placebo in the number of new DU at week 16 [17]. The task force commented on study design, which did not account for DU occurred and healed between visits, and allowed concurrent treatment, but unanimously agreed to maintain only bosentan in the recommendations. A graphic summary of the recommendations on SSc-RP and DU is shown in **Figure 2**.

Pulmonary Arterial Hypertension (PAH)

Combination of PDE-5i (1a) and endothelin receptor antagonists (1a) should be considered as first line treatment of SSc-PAH (A).

This is a new recommendation compared to the 2017 update, supported mainly by two independent post-hoc analyses of the same RCT, the AMBITION trial [21–23]. This was an event-driven double-blind study, in which a heterogeneous population of 500 participants with PAH (CTD and Non CTD) all in WHO functional class II or III, was randomised to receive either ambrisentan 10mg and tadalafil 40mg in combination or the single intervention + placebo in a 2:1:1 ratio. Primary endpoint was Time to first event of clinical failure (TtCF), which was defined as the first occurrence among death, hospitalization for worsening PAH, disease progression, or unsatisfactory long-term clinical response. Coghlan et al published a post-hoc analysis on the 187 patients with CTD-PAH [103 on combination treatment vs 84 on single intervention (44 ambrisentan + 40 tadalafil)] and within this population on the 118 SSc-PAH patients (71 vs 47), adopting the same TtCF endpoint. The benefit of combination treatment was observed both in the CTD and SSc populations against monotherapy groups both singularly or pooled.

Specifically SSc-PAH patients showed a 56% reduction in time to event (HR 0.44 , 95% CI 0.22-0.89), with consistent reductions across single type of events and the secondary endpoints, clearly indicating a superiority of combination treatment vs mono-therapy[22]. From the safety point of view, the most common type of side effect was peripheral oedema present in 45% of patients on combination treatment vs 26 or 33% on ambrisentan or tadalafil monotherapy. Kuwana et al. analysed a modified CTD and SSc-PAH intention to treat population, stratified by baseline characteristics and European Respiratory Society (ERS) risk at baseline (Low/intermediate and high) on the TtCF at 16 weeks. Also in this analysis risk of clinical failure was 53.7% lower in SSc-PAH treated with combination therapy and indicated even higher benefit in patients with low/intermediate risk at baseline or low risk at 16 weeks and no features of left ventricular failure or restrictive lung disease[23]. Smaller prospective controlled

single arm study on treatment naïve patients (N=25) and two retrospective cohort studies (RESCLE and Pharos registries] [24–26] showed comparable benefit of PDE-5i and ERA combination treatment on a variety of hemodynamic features and survival. Based on these studies, as well as metanalysis of the literature [27], the task force unanimously agreed to recommend the use of upfront combination treatment at diagnosis of PAH.

Other Prostacyclin analogues (selexipag) should be considered for the treatment of SSc PAH (B) (1b).

Since the 2017 update, Gaine et al reported the results of a subanalysis of the Griphon study, a phase 3 double blind RCT for selexipag at maximum tolerated dose vs placebo in 1156 patients with PAH either on no treatment or on stable doses of PDE-5i, ERAs or both [28,29]. The 170 patients with SSc-PAH (77 on treatment vs 93 on placebo) had a similar maximum tolerated dose despite slight difference in proportion of background therapy, and showed an overall reduction in risk of morbi/mortality event of 44% (HR 0.56 95 CI 0.34-0.91)[28]. The task force considered the positive results of the sub-analysis although not formally planned in the original study and agreed to recommend the use of Selexipag with strength B (1b).

Methotrexate (1b), mycophenolate mofetil (MMF) (1b) and/or Rituximab (1a) should be considered for treatment of SSc skin fibrosis. (A/B)

This is a new recommendation inviting to consider the use of MMF and/or Rituximab besides MTX for the treatment of skin fibrosis in SSc.

There was no higher level of evidence on MTX compared to the 2017 updates.

The main results informing this recommendation derive from a randomised, double-blind, parallel group trial that enrolled 142 patients with SSc-related interstitial lung disease treated with MMF (target dose 1500 mg twice daily for 24 months) or oral cyclophosphamide (target dose 2 mg/kg per day) for 12 months[43,44,45]. In post-hoc analyses, the joint model identified mRSS improvements from baseline to 24 months in each individual group for both MMF [–4·90, 95% CI −6·4 to −3·4] *and cyclophosphamide* [–5·35, −6·9 to −3·8]). In most patients (26 [69%] of 38 in MMF *vs* 22 [56%] of 39 in cyclophosphamide), the improvements were 5 units or more.

The predominant adverse event was leukopenia that occurred in significantly more patients in the Cyclophosphamide group than the MMF group (30 *vs* 4 patients; p<0·05). Serious adverse events occurred slightly more frequently in the MMF group than the Cyclophosphamide group (n=42 *vs* 36), whereas numerically more serious adverse events in the Cyclophosphamide group (n=8), as compared with the MMF group (n=3), were deemed by the morbidity and mortality committee to be related to the study drug. Later, a post-hoc analysis utilized data from SLSI and SLSII RCTs to study the efficacy of MMF (in SLS-II) on mRSS in comparison with placebo (SLSI)[46]. mRSS improvements exceeding the MCID (≥5.0 units) were observed in 40% of the participants in the CYC arm of SLS I, 37% of the participants in the pooled CYC and MMF arms of SLS-II, and 38% of the participants in the MMF arm of SLS II, compared to 25% of the participants in the placebo arm of SLS I. Moreover, MMF resulted in statistically significant improvements in mRSS in patients with dcSSc when compared with the SLS-I placebo group. Consistent with these findings Naidu et al reported a significant benefit for MMF vs placebo on 24 weeks mRSS (-5 vs -1; p=0.045).

Cyclophosphamide is a cytotoxic agent offered in several connective tissue diseases that was not part of the recommendation statements from the 2017 for skin involvement in SSc. As stated above SLSI and II studies may suggest some benefit although the changes observed in the controlled study (SLSI) vanished after 2 years of follow-up[46]. Moreover, safety profile raised several concerns already commented. Therefore, the task force did not change the previous discussion on Cyclophosphamide for its effects on skin changes. It can be added that one multicentre observational study (ESOS)

including 326 early dcSSc patients showed no significant difference in mRSS across patients treated with MTX (n = 65), MMF (n=118), Cyclophosphamide (n=87), or no immunosuppressants[47]. There was a modest improvement in the mRSS across all groups at 12 months, the least improvement was recorded in the no-immunosuppressant group, who also had the highest mortality.

Since the last update, Rituximab has been investigated in several uncontrolled studies and in 2 RCTs. Rituximab is a chimeric monoclonal antibody that links with CD20 mostly expressed by B-cells. The strongest evidence for Rituximab comes from an investigator initiated double-blind RCT performed in Japan. In this study, 56 SSc patients were included with a mRSS of 10 or greater, an expected survival of at least 6 months[48]. Patients received 4 intravenous doses of the assigned intervention (Rituximab 375 mg/m2 or placebo; once per week for 4 weeks). The absolute improvement in mRSS at 24 weeks was significantly higher in the Rituximab group than in the placebo group (−6·30 vs 2·14; difference −8·44 [95% CI −11·00 to −5·88]; p<0·0001). There was no difference in adverse events.
A smaller (total of 16 patients), 24-month, randomised, double-blind, placebo-controlled, single-centre trial has been reported[48]. Patients with SSc diagnosed <2 years, received intravenous 1000 mg RTX or placebo (0.9% NaCl) on day 1, 15 and at 6 months. The study did not meet its primary endpoint of treatment-related mortality, toxicity, and clinical efficacy (progression-free survival). As secondary endpoints, there were no significant differences in change between baseline and 12-month follow-up of mRSS (placebo −1.8 vs RTX −3.6, p=0.95), but numerically, at 12 months, n=4/8 Rituximab versus n=2/8 in placebo improved >5 points in mRSS. Also in this study, there was no difference in SAEs across groups.
A meta-analysis derived from 24 studies, reported beneficial effects of Rituximab both on skin involvement and Health Assessment Questionnaire Disability Index (HAQ-DI) [49].
The task force considered the totality of the data reviewed above and agreed to recommend the use of Rituximab for the treatment of skin fibrosis in SSc (A) (1a)

Tocilizumab may be considered for the treatment of skin fibrosis in patients with early, inflammatory dcSSc. (C) (1b)

Tocilizumab has been extensively investigated through a clinical development where skin disease was the primary outcome measure. In the phase 2 clinical trial the target population included DcSSc patients with < 5 years disease duration, mRSS >15 and evidence of recent skin progression. Patients also had to show at least one laboratory marker of inflammation [50]. Eighty-seven patients were enrolled and the least squares mean (LSM) change in mRSS at 24 weeks was −3·92 in the Tocilizumab group and −1·22 in the placebo group (difference −2·70, 95% CI −5·85 to 0·45; p=0·0915). The LSM change at 48 weeks was −6·33 in the Tocilizumab group and −2·77 in the placebo group (treatment difference −3·55, 95% CI −7·23 to 0·12; p=0·0579). No significant difference in disability, fatigue, itching, or patient or clinician global disease severity was seen. Fourteen (33%) versus 15 (34%) had serious adverse events. Serious infections were more common in the Tocilizumab group (seven [16%] of 43 patients) than in the placebo group (two [5%] of 44). A phase 3 trial was subsequently performed with similar inclusion criteria for disease activity and skin subset but lower mRSS for inclusion (≥10)[52]. In the 210 individuals enrolled the LSM change in mRSS from baseline to week 48 S was -6·14 for Tocilizumab and -4·41 for placebo (adjusted difference -1·73 [95% CI -3·78 to 0·32]; p=0·10). Change in HAQ-DI and in patient-global and physician-global visual analogue scale assessments did not differ between the 2 arms. Serious adverse events were reported in 13 participants treated with Tocilizumab and 18 with placebo, primarily infections (three events, eight events) and cardiac events (two events, seven events).

Therefore, data from the literature does not support the use of Tocilizumab as first line therapy for skin involvement in early dcSSc considering that the primary endpoint was not met in two international RCTs negative for their primary endpoint (1b)[51-52]. Nevertheless, a trend of benefit

was observed together with a satisfactorily safety profile that led the task force to state that Tocilizumab may be considered for the treatment of skin fibrosis in patients with early, inflammatory dcSSc **(strength C).**

Interstitial Lung Disease (ILD)

MMF (1a), Cyclophosphamide (1a) or Rituximab (1a) should be considered for the treatment of SSc-ILD (A)

As stated above, Mycophenolate Mofetil (MMF) was not part of the last update of the recommendations. SLS II study compared a continuous 24 month course of MMF to a 12 month course of oral Cyclophosphamide (followed by 12 months of placebo) in a randomised, double-blind, parallel group, trial conducted in the USA[45]. Inclusion criteria were SSc with FVC of less than 80% but at least 45%; dyspnoea grade 2 or higher; any ground glass opacity on HRCT whether associated with reticulations (fibrosis) or not; and the onset of first non-Raynaud's symptom within the past 7 years. MMF was administered for a total of 2 years with a target dose of 3g/day. Cyclophosphamide was administered once daily for 12 months, with a target dose of 1.8–2.3 mg/kg. The main result show that the course of the % predicted FVC during the entire 24 months did not differ between the two treatment arms (p=0·24), suggesting a similar efficacy of the two interventions. Each treatment group showed significant improvement in % predicted FVC at 24 months, 2.19% (95% CI 0.53–3.84) for the MMF group and 2.88% (1.19–4.58) for the Cyclophosphamide group. As hypothesized, MMF was better tolerated than Cyclophosphamide based on the time to patient withdrawal, number of treatment failures, and incidence of leucopoenia and thrombocytopenia. The task force noted that SLS studies investigated cyclophosphamide given orally, which may have an increased toxicity (especially bladder) compared to IV route. Nevertheless, it was also noted that there is insufficient data to compare the risk/benefit ratio of oral versus IV route for the treatment of SSc-ILD, which meant we were unable to recommend a specific route of administration.
Although comparing patients from distinct trials entails inherent limitations, SSc-ILD patients included in the placebo arm of SLS I have been compared to patients from the MMF arm of SLS II in post-hoc analyses[54]. After adjustment for baseline disease severity, treatment with MMF in comparison with placebo was associated with improved % predicted FVC (+3.26+/-1.06 versus -2.18 +/-1.44; P < 0.0001). Overall, 64.4% of MMF patients had improvement in FVC whereas 28.8 % of placebo patients had FVC improvement.
Based on these data, and on data from SENSCIS trial discussed below, the task force agreed to recommend both MMF and Cyclophosphamide for the treatment of SSc-ILD (A).

The RECITAL trial compared Rituximab to intravenous Cyclophosphamide in a basket design including ILD related to 3 CTDs (97 patients including 37 SSc)[55]. The design was a double-blind, double-placebo, phase 2b trial to assess the superiority of Rituximab compared with Cyclophosphamide. Patients were randomly assigned (1:1) to receive Rituximab (1000 mg at weeks 0 and 2 intravenously) or Cyclophosphamide (600 mg/m^2body surface area every 4 weeks intravenously for six doses). At week 24, the unadjusted mean change from baseline in FVC was a gain of 99 mL (SD 329; relative change 4.35% [SD 15·67]) in the Cyclophosphamide group and 97 mL (234; 4.31% [11·80]) in the Rituximab group. Using a mixed-effects model adjusted for age, sex, baseline FVC, and diagnosis, the difference in 24-week rate of change in FVC from baseline in the Rituximab group versus the Cyclophosphamide group was –40 mL (95% CI –153 to 74; p=0·49). The task force noted that the effects of treatment were consistent across the three different CTD subgroups. More adverse events were reported in the Cyclophosphamide group (646 events) than in the Rituximab group (445 events).
In the phase 2 DESIRES clinical trial that primarily investigated skin, 86% of the patients had ILD on HRCT with baseline FVC being 88% in the RTX group and 89% of predicted value in the placebo arm[47]. The predicted FVC at 24 weeks compared to baseline was significantly improved in the Rituximab

group compared with the placebo group (0·09% vs –2·87%; difference 2·96%[95%CI0·08–5·84];p=0·044). A similar trend was observed in subgroup analyses of patients with baseline FVC% predicted less than 80% and patients with disease duration less than 5 years.

An open label, randomized, controlled trial in 60 patients with early DcSSc and ILD compared IV Cyclophosphamide (500 mg/m2) to Rituximab (two courses of 1000 mg)[56]. The primary outcome was FVC changes at 6 months. SSc-ILD patients had a severe involvement with baseline FVC of 61.30 (11.28) % in the RTX group and 59.24 (12.96) % in the Cyclophosphamide group with an extent of ILD on HRCT > 20% in 83% of the patients in each arm. There was a significant improvement in the predicted FVC in the RTX group [from 61.30 (11.28) to 67.52 (13.59); *P* = 0.002] while in the CYC group FVC had an insignificant decrease [from 59.25 (12.96) to 58.06 (11.23); *P* = 0.496]. Mean difference in FVC predicted was in favour of RTX group and was 9.46 (95% CI: 3.01, 15.90; *P* = 0.003).

Further, a meta-analysis looking at the effects of Rituximab on SSc-ILD identified 20 studies (2 randomized controlled trials, 6 prospective studies, 5 retrospective studies and 7 conference abstracts) comprising a total of 575 SSc-ILD patients[57]. RTX improved FVC from baseline by 4.49% (95% CI 0.25, 8.73) at 6 months and by 7.03% (95% CI 4.37, 9.7) at 12 months. Moreover, patients treated with RTX had a lower risk of developing infections compared with controls [OR 0.256 (95% CI 0.104, 0.626), I2 = 0%, P = 0.47).

In summary, since the last recommendations, Rituximab showed its benefit in a phase 2 trial in which ILD was a secondary outcome measure, it showed superiority to Cyclophosphamide in small RCT in patients with advanced ILD, a meta-analysis of various studies confirmed efficacy on lung outcomes and in a basket CTD-ILD trial it showed similar effects to Cyclophosphamide but with a better safety profile. Therefore, the task force recommends that Rituximab should be considered for the treatment of SSc-ILD (A).

Nintedanib should be used alone or in combination with MMF for the treatment of SSc ILD (A) (1a)

Since the last update of the recommendations, the largest clinical trial ever conducted in SSc investigated the effects of the tyrosine-kinase inhibitor Nintedanib[58]. It was a phase 3 clinical trial that recruited 576 SSc-ILD patients. Patients had a disease with an onset of the first non-Raynaud's symptom within the past 7 years and a high-resolution computed tomographic scan that showed fibrosis affecting at least 10% of the lungs. Patients were randomly assigned, in a 1:1 ratio, to receive 150 mg of Nintedanib, administered orally twice daily, or placebo. In the primary end-point analysis, the adjusted annual rate of change in FVC was -52.4 ml per year in the Nintedanib group and -93.3 ml per year in the placebo group (difference, 41.0 ml per year; 95% confidence interval [CI], 2.9 to 79.0; P = 0.04). Other pre-specified endpoints on dyspnoea or PROs were not met. The percentage of patients who had an adverse event that led to the discontinuation of the assigned intervention was higher in the Nintedanib group than in the placebo group (16.0% vs. 8.7%). Diarrhoea, the most common adverse event, was reported in 75.7% of the patients in the Nintedanib group and in 31.6% of those in the placebo group. Several additional studies have been done and one may highlight that patients at risk of ILD progression benefited from Nintedanib largely irrespective of their extent of fibrotic ILD at baseline. In at-risk of progression patients[59], Nintedanib reduced the rate of FVC decline across subgroups, with a numerically greater effect in patients with these risk factors for rapid FVC decline. The open label extension study (additional 52 weeks) showed from 197 patients in the continued Nintedanib group and 247 in the initiated Nintedanib group that the safety profile of Nintedanib over 52 weeks of SENSCIS-ON was consistent with that reported in SENSCIS[60]. The change in FVC over 52 weeks of SENSCIS-ON was similar to that observed in the Nintedanib group of SENSCIS.

Importantly, patients included in the SENSCIS trial were stratified by the use of MMF and pre-planned sub-analysis included evaluation of primary endpoint in MMF subgroups[61]. At baseline, 139 (48%) participants in the Nintedanib group and 140 (49%) in the placebo group were taking mycophenolate. Although the absolute effect of Nintedanib versus placebo on reducing the rate of decline in FVC was numerically lower in participants who were taking mycophenolate at baseline than in those who were not, the relative treatment effect of Nintedanib was similar between these subgroups (40% for those taking mycophenolate at baseline and 46% for those not taking mycophenolate at baseline) and consistent with that observed in the overall population (44%). The treatment effect of Nintedanib on the annual rate of FVC decline was numerically greater in participants who were not taking mycophenolate at baseline (difference: 55·4 mL per year [95% CI 2·3 to 108·5]) than in those who were taking mycophenolate (26.3 mL per year [–27.9 to 80.6]. The adverse event profile of Nintedanib was generally similar in the subgroups by mycophenolate.

The SENSCIS trial was completed by the INBUILD trial assessing Nintedanib in miscellaneous progressive fibrosing ILD (PF-ILD). In this phase-3 trial, patients were assigned to receive Nintedanib (150 mg twice daily) or placebo while background immunosuppressants at inclusion were not allowed[62]. It is important to note that the inclusion criteria of INBUILD built the foundation for the definition of PF-ILD, formally agreed by consensus only in 2020 [63] An enrichment strategy was used, and two thirds of the patients had a Usual Interstitial pneumonia (UIP) like fibrotic pattern. Among 170 patients with autoimmune disease-related ILDs (including 39 SSc-ILD), the rate of decline in FVC over 52 weeks was -75.9 ml/year with Nintedanib versus -178.6 ml/year with placebo (difference 102.7 ml/year [95% confidence interval 23.2, 182.2]; nominal P = 0.012). No heterogeneity was detected in the effect of Nintedanib versus placebo across subgroups based on ILD diagnosis (P = 0.91). As reported in the SENSCIS trial, diarrhoea was the most frequent AE reported in 63.4% and 27.3% of subjects in the Nintedanib and placebo groups, respectively.

Considering the results of the SENSCIS and INBUILD trials and the above commented results about the subgroup of concomitantly mycophenolate treated patients, the task force recommends that Nintedanib should be considered alone or in combination with MMF for the treatment of SSc ILD (A)

<u>Tocilizumab should be considered for the treatment of SSc-ILD (B) (1b)</u>

Within the two trials having mRSS as primary endpoint discussed above, changes in FVC were assessed as secondary endpoint[51–53]. In the phase 2 trial 87 patients were randomized to either Tocilizumab of placebo, in the absence of any background immunosuppressive treatment, which was allowed only after week 24 as escape in case of skin or lung worsening[51]. The 24 weeks analysis clearly showed significantly smaller decrease in FVC for Tocilizumab than for placebo from baseline (Tocilizumab –34 mL *vs* placebo –171 mL; least square mean difference 136 mL, 95% CI 9 to 264; p=0·0368) which became not significant at 48 weeks. The phase 3 RC, within slight changes in target population described above, 212 individuals were randomly assigned to receive again either weekly subcutaneous placebo (107) or 162 mg of Tocilizumab (105). At week 48, the LSM change from baseline in FVC% predicted was –4.6 in the placebo group and –0.4 in the Tocilizumab group (difference 4·2 [95% CI 2·0–6·4]; nominal p=0·0002). Based on a prespecified exploratory analysis, 15 (17%) of 91 participants in the placebo group and 5 (5%) of 93 in the Tocilizumab group had an absolute decline in FVC of at least 10%. Based on these data the FDA approved the use of Tocilizumab for the treatment of SSc-ILD. The task force acknowledged that ILD was not the primary objective of both main Tocilizumab trials although it was pre-specified as secondary outcome in the phase 3 trial, the magnitude of effect between the 2 arms was large and drug was investigated against no background treatment in an “early, inflammatory” population. As a result of discussion, the task force agreed to recommend that Tocilizumab should be considered for the treatment of SSc-ILD (grade B). A diagram summarizing different options of SSc-ILD treatment is shown in **Figure 4**

Available evidence for the use of oral or IV steroids for the treatment of SSc ILD was explored in the SLR but no sufficient evidence (2b) was retrieved to propose a specific statement in SSc-ILD[10]. Due to this lack of evidence, the task force unanimously agreed not to formulate any recommendation for or against the use of steroids in SSc-ILD.

High intensity immunosuppression in patient with poor prognosis

High Intensity immunosuppression (usually including Cyclophosphamide) followed by autologous Hematopoietic Stem Cell Transplant (HSCT) may be considered for the treatment of selected patients with early severe dcSSc and poor prognosis, in the absence of advanced cardio-respiratory involvement. (A)

This recommendation is essentially unchanged since the 2017 updates[7]. Since the previous literature review the SCOT study (Scleroderma Cyclophosphamide or Transplantation) reported the 54 months beneficial effect of autologous HSCT on a combined morbi-mortality event[64]. Specifically, the target population included 75 patients with dcSSC of up to 5 years disease duration and evidence of lung involvement as assessed by diagnosis of ILD or previous renal involvement, and excluded patients with severe lung, heart, or renal involvement (DLCO <40% or FVC <45% or diagnosis of PAH). Patients with GAVE or previous use of Cyc were also excluded. Patients were randomized 1:1 to receive either Cyclophosphamide (500-750mg/square meter) for 12 months or high dose Cyclophosphamide (120 mg/kg) + equine ATG + total body irradiation, preceded by bone marrow mobilization and leukapheresis and followed by auto transplant of hematopoietic stem cells (Median 5.6 million CD34+ cells/kg). The study endpoint was the Global Ranked Composite Score (GRCS), whereas each participant was scored against all participants of the other arm and ranked according to the occurrence of death, organ failure (respiratory, renal or cardiac) , drop in FVC of at least 10% , worsening (>0.4) of HAQ-DI, or increase of at least 25% of mRSS, in this order of importance. The GRCS allowed 1404 comparisons 67% of which were in favour of patients in the transplant arm vs 33% in favour of patients in the Cyclophosphamide arm (p=0.01). The event-free survival analysis showed accordingly, that 74% of patients in the transplant arm remained event free at month 72 vs 47% of patients in the Cyclophosphamide arm. Further only 9% of patients initiated any DMARD by month 54 in the transplant arm vs 44% of patients in the Cyclophosphamide arm. Treatment related mortality was 3% at 54 months vs 0% in the Cyclophosphamide arm. The results of this study were consistent with the long term analysis of the ASTIS trial (informing the previous set of recommendations) published by Ait Abdallah et al. [65,66]. In this prospective cohort study on 49 subjects, the analysis at 60 months favoured the transplant arm both as far as GRCS (p=0.018) and event free survival (73% vs 44.9%, p=0.06). The task force acknowledged that HSCT was never compared with other means of immunosuppression or targeted therapies and that treatment related mortality needs to be carefully considered above all in patients with suboptimal cardiac function, but the unambiguous efficacy of the intervention has informed this recommendation with strength A.

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- 1 EULAR Methodologist
- 1 HPRT
- 4 Fellows (SLR)
- 1 Librarian
- 2 patient representatives