Update of EULAR recommendations for the treatment of systemic sclerosis


ABSTRACT
The aim was to update the 2009 European League against Rheumatism (EULAR) recommendations for the treatment of systemic sclerosis (SSc), with attention to new therapeutic questions. Update of the previous treatment recommendations was performed according to EULAR standard operating procedures. The task force consisted of 32 SSc clinical experts from Europe and the USA, 2 patients nominated by the pan-European patient association for SSc (Federation of European Scleroderma Associations (FESCA)), a clinical epidemiologist and 2 research fellows. All centres from the EULAR Scleroderma Trials and Research (EUSTAR) were invited to submit and select clinical questions concerning SSc treatment using a Delphi approach. Accordingly, 46 clinical questions addressing 26 different interventions were selected for systematic literature review. The new recommendations were based on the available evidence and developed in a consensus meeting with clinical experts and patients. The procedure resulted in 16 recommendations being developed (instead of 14 in 2009) that address treatment of several SSc-related organ complications: Raynaud’s phenomenon (RP), digital ulcers (DUs), pulmonary arterial hypertension (PAH), skin and lung disease, scleroderma renal crisis, and gastrointestinal involvement. Compared with the 2009 recommendations, the 2015 recommendations include phosphodiesterase type 5 (PDE-5) inhibitors for the treatment of SSc-related RP and DUs, riociguat, new aspects for endothelin receptor antagonists, prostacyclin analogues and PDE-5 inhibitors for SSc-related PAH. New recommendations regarding the use of fluoxetine for SSc-related RP and haematopoietic stem cell transplantation for selected patients with rapidly progressing SSc were also added. In addition, several comments regarding other treatments addressed in clinical questions and suggestions for the SSc research agenda were formulated. These updated data-derived and consensus-derived recommendations will help rheumatologists to manage patients with SSc in an evidence-based way. These recommendations also give directions for future clinical research in SSc.

INTRODUCTION
Systemic sclerosis (SSc) is a connective tissue disease (CTD) which affects skin, blood vessels, heart, lungs, kidneys, gastrointestinal (GI) tract and musculoskeletal system. Involvement of internal organs results in significant morbidity and mortality of patients with SSc. Clinical complexity and heterogeneity of SSc leaves treatment of this disease very challenging.1 Establishing the first European League against Rheumatism (EULAR) recommendations for the treatment of SSc in 2009 was therefore a milestone for improving care of patients with SSc and they were well received by the international community of scleroderma experts.2 3 In view of several recent developments regarding treatment of SSc-related internal organ involvement, the need of an update of the 2009 EULAR recommendations has been recognised by the EULAR Scleroderma Trials and Research (EUSTAR) group and acknowledged by the EULAR. Following EULAR standardised operating procedures, an ad hoc expert committee was established by EULAR and EUSTAR.4 5 As in previous recommendations, the global community of SSc experts cooperating within EUSTAR was involved.6

Based on the published evidence and expert opinion, 16 updated recommendations regarding pharmacological treatment of SSc-specific organ involvement were formulated. It should be recognised that the field of management of patients with SSc is larger than pharmacological management alone. Management of SSc also includes (early) diagnosis of the disease, early diagnosis of internal organ involvement, identification of patients at risk of development of new organ complications and deterioration of the disease, as well as non-pharmacological treatments, of which most of are beyond the scope of this project. There are also several (potential) drugs, including new promising therapies that might be helpful in management of patients with SSc that could not be included in these evidence-based recommendations due to insufficient data at present. The actual recommendations are

aimed to guide pharmacological treatment of SSc-specific organ involvement. These recommendations are not meant to replace the physician’s clinical judgement or the patient–physician shared decision. They should be viewed in light of the clinician’s understanding of the individual patient and the clinician’s and patients’ judgement of the balance between the efficacy and toxicity of a treatment. Although some treatment-related toxicities are mentioned in the text of the recommendations, it still is the responsibility of the physician to recognise and monitor all possible toxicities/side effects according to the information supplied by the producer and all other available sources.

METHODS

Design
These recommendations are an update of the 2009 EULAR recommendations for treatment of SSc.6 Evidence for existing recommendations was updated with new evidence published since then, all existing recommendations were newly judged, and reformulated if necessary. Existing recommendations could also be removed, for instance when a certain (class of) drugs was withdrawn from the market. New evidence-based recommendations were added.

Expert panel
An expert panel was established with 32 clinical experts in the field of SSc (29 rheumatologists, 1 dermatologist, 2 paediatric rheumatologists with expertise in juvenile SSc), 2 patients with SSc (KF, JW) and 1 clinical epidemiologist (JF) overall representing 11 countries. The clinical experts had to be internationally recognised as specialists in SSc with several years of experience in diagnosing and treating patients with this disease. The two patient partners were nominated by the pan-European patient association for SSc (FESCA). Unfortunately, at the time of formation of the task force, we were unable to identify health professional with experience in treating patients with SSc capable of taking part in the work. Potential conflicts of interest were declared by all participants. There was no involvement of third parties in the entire process of making these recommendations.

Selection process of clinical questions
To create a comprehensive list of topics of interest, clinical experts from all EUSTAR centres were asked by e-mail to contribute clinical questions relevant to the pharmacological treatment of SSc. As a result, 170 clinical questions were provided by experts from 41 EUSTAR centres. These questions were then categorised by drug (class) and aggregated with the clinical questions from 2009; duplicates were removed. The clinical questions were phrased according to the ‘PICO’ format (Patients, Intervention, Comparator, Outcome). Subsequently, the clinical questions were submitted in a three-round web-based Delphi exercise to members of EUSTAR centres, as previously described. The Delphi exercise was completed until May 2014. For more details regarding the Delphi exercise please see the online supplementary material.

The results of the Delphi exercise were presented to the expert panel in a first face-to-face meeting in June 2014. In this meeting, the nominal group technique was used, based on the results of the Delphi exercise. Finally the clinical questions were selected that were subjected to the systematic literature search (see online supplementary table S1).

Systematic literature search
The systematic literature search was performed by two fellows (AK, MB) supervised by a task force member (JA), guided by the clinical epidemiologist (JF). For new clinical questions, the literature search was performed on all articles published between 1966 and, as agreed by the panel, until 30 September 2014 in PubMed, EMBASE, the Cochrane Database for meta-analyses and the Cochrane Controlled Trials Register as well as the 2012 and 2013 EULAR and American College of Rheumatology (ACR) congress abstract archives. For clinical questions already included in the existing recommendations, the same strategy was followed, searching from February 2007 to 30 September 2014. A standardised search strategy was used for all clinical questions (see online supplementary table S2).

One meta-analysis, including eight randomised controlled trials (RCTs): seven with nifedipine and one with nicardipine, with 109 patients with SSc involved, indicated that dihydropiridine-type calcium antagonists reduce the frequency and severity of ischaemic attacks in SSc-RP.8–13 The weighted mean difference (WMD) of all calcium antagonists versus placebo (six trials) for
The updated EULAR recommendations for treatment of systemic sclerosis, according to the organ involvement, including strength of the evidence and the results of internal evaluation within the task force group.

<table>
<thead>
<tr>
<th>Organ involvement</th>
<th>Recommendation</th>
<th>Level of evidence</th>
<th>Strength of recommendation</th>
<th>Results of internal evaluation</th>
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<tbody>
<tr>
<td>I. SSc-RP</td>
<td>Dihydropyridine-type calcium antagonists, usually oral nifedipine, should be considered for first-line therapy for SSc-RP. PDE-5 inhibitors should also be considered in treatment of SSc-RP. Intravenous iloprost should be considered for severe SSc-RP. Experts recommend that intravenous iloprost should be used for treatment of SSc-RP attacks after oral therapy. Fluoxetine might be considered in treatment of SSc-RP attacks.</td>
<td>1A</td>
<td>A</td>
<td>8.19</td>
</tr>
<tr>
<td>II. Digital ulcers in patients with SSc</td>
<td>Intravenous iloprost should be considered in the treatment of digital ulcers in patients with SSc. PDE-5 inhibitors should be considered in the treatment of digital ulcers in patients with SSc. Bosentan should be considered for reduction of the number of new digital ulcers in SSc, especially in patients with multiple digital ulcers despite use of calcium channel blockers, PDE-5 inhibitors or iloprost therapy.</td>
<td>1B</td>
<td>A</td>
<td>8.39</td>
</tr>
<tr>
<td>III. SSc-PAH</td>
<td>ERA, PDE-5 inhibitors or riociguat should be considered to treat SSc-related PAH. Intravenous epoprostenol should be considered for the treatment of patients with severe SSc-PAH (class III and IV). Prostacyclin analogues should be considered for the treatment of patients with SSc-PAH.</td>
<td>1B</td>
<td>B</td>
<td>8.32</td>
</tr>
<tr>
<td>IV. Skin and lung disease</td>
<td>Methotrexate may be considered for treatment of skin manifestations of early diffuse SSc. In view of the results from two high-quality RCTs and despite its known toxicity, cyclophosphamide should be considered for treatment of SSc-ILD, in particular for patients with SSc with progressive ILD. HSCT should be considered for treatment of selected patients with rapidly progressive SSc at risk of organ failure. In view of the high risk of treatment-related side effects and of early treatment-related mortality, careful selection of patients with SSc for this kind of treatment and the experience of the medical team are of key importance.</td>
<td>1B</td>
<td>A</td>
<td>8.03</td>
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<tr>
<td>V. SRC</td>
<td>Experts recommend immediate use of ACE inhibitors in the treatment of SRC. Blood pressure and renal function should be carefully monitored in patients with SSc treated with glucocorticoids.</td>
<td>3</td>
<td>C</td>
<td>8.52</td>
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<tr>
<td>VI. SSc-related gastrointestinal disease</td>
<td>PPI should be used for the treatment of SSc-related gastro-oesophageal reflux and prevention of oesophageal ulcers and strictures. Prokinetic drugs should be used for the management of SSc-related symptomatic motility disturbances (dysphagia, GERD, early satiety, bloating, pseudo-obstruction, etc). Intermittent or rotating antibiotics should be used to treat symptomatic small intestine bacterial overgrowth in patients with SSc.</td>
<td>1A</td>
<td>C</td>
<td>8.58</td>
</tr>
</tbody>
</table>

ACE, angiotensin converting enzyme; ERA, endothelin receptor antagonist; EULAR, European League against Rheumatism; GERD, gastroesophageal reflux disease; HSCT, haematopoietic stem cell transplantation; ILD, interstitial lung disease; PAH, pulmonary arterial hypertension; PDE-5, phosphodiesterase type 5; PPI, proton pump inhibitors; RCT, randomised controlled trial; SRC, scleroderma renal crisis; SSc, systemic sclerosis; SSc-RP, Raynaud phenomenon in patients with systemic sclerosis.

Box 1 Research agenda

1. Evaluation of the efficacy and safety of cyclophosphamide in the treatment of early diffuse systemic sclerosis (SSc);
2. Evaluation of the efficacy and safety of mycophenolate motefil and azathioprine in the treatment of SSc;
3. Evaluation of the efficacy and safety of anti-CD20 therapies in the treatment of SSc;
4. Evaluation of calcium antagonists in the prevention of SSc-related pulmonary arterial hypertension;
5. Evaluation of calcium antagonists in the treatment of digital ulcers in SSc;
7. Evaluation of the efficacy and safety of ACE inhibitors in the prevention of scleroderma renal crisis;
8. Evaluation of the efficacy of non-pharmacological treatments in SSc.

The reduction in the number of ischaemic attacks over a 2-week period was −8.31 (95% CI −15.71 to −0.91). When the five RCT evaluating nifedipine (10–20 mg three times a day) versus placebo were analysed separately, the reduction was greater with a WMD of −10.21 (95% CI −20.09 to −0.34).

None of the studies included into meta-analysis has directly examined the side effects of calcium antagonists in SSc. Hypotension, dizziness, flushing, dependent oedema and headaches are believed to be fairly common side effects of these agents.8

Another meta-analysis of six RCTs (two with sildenafil, three with tadalafil and one with vardenafil) including 236 patients with CTD-related RP, of whom 95% were patients with SSc, showed that PDE-5 inhibitors improve frequency, severity and duration of RP attacks.16–22 The treatment effect (mean difference; 95% CI) for daily frequency (−0.49; −0.71 to −0.28), severity (−0.46; −0.74 to −0.17) and daily duration of RP (−14.62; −20.25 to −9.00 min) although significant was only moderate.
Side effects associated with usage of PDE-5 inhibitors were common and include different forms of vasomotor reactions, myalgia, allergic reaction, chest pain, dyspepsia, nasal stuffiness and visual abnormalities.

Considering long-term experience and good safety profile, experts recommend that calcium channel blockers should be used as first line therapy for SSc-RP and PDE-5 inhibitors in patients with SSc with severe RP and/or those who do not satisfactorily respond to calcium channel blockers.

Recommendation: Intravenous iloprost should be considered for severe SSc-RP (strength of recommendation: A).

Experts recommend that intravenous iloprost should be used for treatment of SSc-RP attacks after oral therapy.

One meta-analysis, including five RCTs with intravenous iloprost, one RCT with oral iloprost and one RCT with oral cisaprost, with 332 patients with SSc in total, indicates that iloprost is effective in reducing the frequency and severity of SSc-RP.31-33

Iloprost, given intravenously (0.5–3 ng/kg/min for 3–5 consecutive days sequentially) or orally (50–150 µg twice a day) significantly reduced the frequency of ischaemic attacks, and improved the RP severity score in comparison with placebo (WMD; 95% CI 17.46; 19.19 to 15.73 and −0.69; 1.12 to −0.26, respectively). Oral prostanooids seem to be generally less effective than intravenous iloprost in the treatment of SSc-RP, although some beneficial effects could be seen with higher doses.34-36

Two RCTs comparing intravenous iloprost (0.5–2 ng/kg/min for 3–5 days, every 6–8 weeks) with nifedipine (30–60 mg/day) indicate that iloprost is only slightly superior to nifedipine in improving symptoms of SSc-RP.37-39

In view of costs and feasibility, the experts recommended that intravenous prostanooids are considered when oral therapies (including calcium channel blockers and PDE-5 inhibitors) have failed. As most drugs used for treating RP may induce vascular side effects, the experts recommend particular attention if prostanooids are combined with other vasodilators.

Recommendation: Fluoxetine might be considered in treatment of SSc-RP attacks (strength of recommendation: C).

One small study including subgroup analysis of 27 patients with SSc-related RP indicates that fluoxetine (orally 20 mg/day) was superior to nifedipine LA (orally 40 mg/day) in reduction of severity of RP and comparable with nifedipine in reduction of frequency of RP attacks in patients with SSc.40 The latter effect was not significant in patients with SSc neither for fluoxetine nor for nifedipine, which could be due to the low number of patients with SSc included. Safety results, available for the combined group of patients with primary RP (n=26) and SSc-related RP (n=27) indicated that fluoxetine was better tolerated than nifedipine: withdrawals due to adverse effects were more than twice higher in the nifedipine group as compared with fluoxetine. Main reasons leading to treatment withdrawals in the fluoxetine group were: apathy, lethargy and impaired concentration.

Despite the relatively low quality of published evidence, experts recognise that fluoxetine is used in practice and believe that fluoxetine is a useful alternative for treatment of SSc-RP in particular in patients with SSc who cannot tolerate or do not respond to vasodilators.

Since the data regarding the use of fluoxetine in patients with SSc is limited and fluoxetine, as a serotonin-specific reuptake inhibitor and antidepressant, may have potential effects on the central nervous system or heart, it is important to consider potential contraindications before starting treatment and to carefully monitor patients for side effects when on fluoxetine, in particular during long-term treatment.41 Of note, withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt.

II. DUs in patients with SSc
Recommendation: Intravenous iloprost should be considered in the treatment of DUs in patients with SSc (strength of recommendation: A).

Intravenous iloprost (0.5–2 ng/kg/min for 3–5 consecutive days) significantly reduced the number of DUs in comparison with placebo in one small RCT (Jadad score 3), and improved DUs healing in another RCT (Jadad score 4) including 73 patients with SSc with active DUs (p=0.06 vs placebo for 50% improvement).37-38 In addition, two RCTs comparing intravenous iloprost with oral nifedipine suggest that both medications have a beneficial effect on DUs but the number of patients with DUs in both trials was small.39-40

One meta-analysis published in 2013 included, in addition to the two aforementioned RCTs with intravenous iloprost, two additional RCTs, one with oral iloprost (100 or 200 µg/day vs placebo for 6 weeks) and one with oral treprostinil (slow release up to 16 mg twice daily for 20 weeks).32-37 38 This analysis revealed a trend towards a beneficial effect of prostanooids over placebo for healing of DUs (the pooled risk ratio (RR); 95% CI for number of patients with DUs improvement or healing (1.33; 0.97 to 1.84, p=0.08).38 The greatest mean effect was seen with intravenous iloprost (RR; 95% CI 3.00; 0.76 to 11.81).

The results of this meta-analysis summarising the effect of four RCTs (two with intravenous iloprost, one with oral iloprost and one with oral beraprost) did not show significant effects of prostanoids for the prevention of new DUs in SSc (RR; 95% CI for number of patients with new DUs: 0.85; 0.68 to 1.08, p=0.19).38 Again, the greatest effect was seen with intravenous iloprost (RR; 95% CI 1.18; 0.30 to 4.72). When the results of the small study by Wigley et al42 were evaluated separately, they suggest that intravenous iloprost may prevent new DUs in patients with SSc (standardised mean difference (SMD); 95% CI for number of DUs: −0.77; −1.46 to −0.08, p=0.03).38 Moreover, an RCT with epoprostenol, administered continuously for severe SSc-related PAH (SSc-PAH), revealed a tendency towards a reduction in the number of new DUs (by 50%).

Considering the fact that oral prostanoids showed lower efficacy for treatment of SSc-related RP, as compared with intravenous iloprost (see section on RP), the experts decided, based on the results of the aforementioned two RCTs, to recommend intravenous iloprost as a treatment for DUs in patients with SSc. Further studies are required to confirm beneficial effect of intravenous iloprost in prevention of development of DUs in patients with SSc. In view of risk of side effects and route of administration usually requiring hospitalisation, intravenous iloprost should be considered in particular in patients with SSc with DUs not responding to oral therapy. In severe cases, combination therapy with oral vasodilator and intravenous iloprost can be used. However, the increased risk of side effects should be taken into account.

Recommendation: PDE-5 inhibitors should be considered in the treatment of DUs in patients with SSc (strength of recommendation: A).

One meta-analysis of three RCTs investigating various selective PDE-5 inhibitors (sildenafil 50 mg twice daily, modified release sildenafil 100 mg/day increased up to 200 mg/day or tadalafil 20 mg on alternate days) in patients with SSc with RP of whom 39 had baseline DUs indicated that selective PDE-5 inhibitors improve healing of DUs in patients with SSc.39 Although DUs healing was a co-primary outcome only in one of
three RCTs included into the meta-analysis, and all three RCTs were underpowered to detect difference between active treatment and placebo, the pooled effect shows significant benefit of PDE-5 inhibitors over placebo on DU healing.\(^{39}\) Both the number of patients with DU healing and the number of patients with DU improvement were significantly higher for PDE-5 inhibitors as compared with placebo (RR; 95% CI 3.28; 1.32 to 8.13, \(p<0.01\) for DU healing and 4.29; 1.73 to 10.66, \(p<0.002\) for DU improvement, respectively).\(^{38}\) The results of this meta-analysis are corroborated by an independent multicentre RCT evaluating the effect of tadalafil (20 mg/day on alternate days for 8 weeks as an add-on-therapy to previous vasodilators) on DU healing, as one of two co-primary end points together with effect on RE in 31 patients with SSc with baseline DUs.\(^{37}\) After 8 weeks of treatment, DUs healed completely in 14 out of 18 patients in the tadalafil group as compared with 5 out of 13 patients in the placebo arm (\(p<0.05\)). The results of this study including altogether 53 patients with SSc with SSc-related RP indicate that tadalafil was also associated with significantly lower risk of new DUs: new DUs developed in 1 out of 27 patients from the tadalafil group as compared with 9 out of 26 patients from the placebo group (\(p<0.05\)). Tadalafil (20 mg/day on alternate days for 6 weeks with 1 week wash out period, as add-on-therapy to previous vasodilators) prevented development of new DUs in another single-centre cross-over RTC including 24 patients with SSc with secondary RP (95% of whom had SSc, cited in the meta-analysis by Tingley et al.\(^{20,}\)\(^{38}\)\) In this study, only 1 new DU developed under tadalafil treatment as compared with 13 new DUs which developed in six patients under placebo treatment (\(p<0.05\)).

Side effects of PDE-5 inhibitors are discussed in the previous paragraph regarding PDE-5 inhibitors in the treatment of RP.

Based on these data, the experts concluded that PDE-5 inhibitors can be efficacious in treating SSc-related DUs. Whether other than tadalafil PDE-5 inhibitors can prevent development of new DUs in patients with SSc needs to be clarified in further studies.

Annotation: The recently published SEDUCE trial did not reach statistical significance with respect to the influence of sildenafil (20 mg three times daily for 12 weeks) on time to DU healing, in part due to unexpectedly high healing rates in placebo group.\(^{39}\) The study did show significant reduction in the number of DUs per patient at week 8 (1.23±1.61 in sildenafil group vs 1.79±2.40 in placebo group, \(p=0.04\)) and week 12 (0.86±1.62 vs 1.51±2.68, \(p=0.01\), respectively) as a result of a greater healing rate. Since the experts discussed the impact of the study not unambiguously, and the sildenafil dose used in SEDUCE study was lower than in the studies included in the aforementioned meta-analysis by Tingley et al.,\(^{38}\) the results of this study, which was published after data closure for the recommendations, did not change the respective recommendation.\(^{39}\)

Recommendation: Bosentan should be considered for reduction of the number of new DUs in SSc, especially in patients with multiple DUs despite use of calcium channel blockers, PDE-5 inhibitors or iloprost therapy (strength of recommendation: A).

The effect of bosentan, a dual receptor antagonist, on DUs prevention and healing was evaluated in two high-quality RCTs (RAPIDS-1 and RAPIDS-2) including altogether 310 patients with SSc with a history of or at least one active DUs at baseline. Bosentan, given orally at a dose of 62.5 mg twice a day for 4 weeks followed by 125 mg twice a day for 12 weeks in RAPIDS-1 or 20 weeks in RAPIDS-2, significantly reduced the number of new DUs in both trials.\(^{40,\)\(^{41}\) In a recent meta-analysis of RAPIDS-1 and RAPIDS-2, treatment with bosentan was associated with a significant reduction in the mean number of new DUs per patient in the overall trials population (SMD; 95% CI −0.34; −0.57 to −0.11, \(p=0.004\)) and in patients with SSc with baseline DUs (SMD; 95% CI −0.36; −0.61 to −0.11, \(p=0.005\)).\(^{38}\) The effect of bosentan was most pronounced in patients with SSc with multiple (four or more) DUs at baseline (effect size (ES); 95% CI =0.52; −1.01 to −0.02) as compared with patients with SSc with lower number of DUs at baseline (ES; 95% CI −0.08; −0.44 to 0.28) in RAPIDS-2.\(^{41}\)

The reduction in the number of patients with a new DU was not statistically significant in any of the RAPIDS trials or their meta-analysis.\(^{40}\)\(^{41}\)

Neither trial indicated that bosentan is superior to placebo in the healing of SSc-related active DUs, as evaluated by the time to complete or partial healing of DUs present at baseline, the time to healing of all DUs, or the percentage of patients with complete DU healing (\(p>0.05\) vs placebo for all comparisons). At present, there is insufficient evidence that endothelin receptor antagonists (ERA) have beneficial effects on SSc-RP attacks either.

There are two major concerns related to the use of bosentan and other ERA: potential liver injury and teratogenicity. Hormonal contraceptives may not be reliable if co-administered with bosentan, because bosentan may reduce their efficacy by interference with the cytochrome P450 system.

In view of the results of both RAPIDS trials and considering potential toxicities associated with bosentan, experts recommend usage of bosentan especially in patients who have multiple DUs despite treatment with other vasodilators such as calcium channel blockers, PDE-5 inhibitors and iloprost to prevent the development of new DUs.

The results of the RAPIDS-2 trial which were published in full in 2011 did not support the difference in response to bosentan between patients with limited and diffuse SSc subsets, an aspect, which was suggested by the subanalysis of the RAPIDS-1 trial.\(^{40}\)\(^{41}\) Because of these data, the experts decided that in the present recommendations bosentan should be considered for reduction of new DUs in all patients with SSc with independent of the disease subset.

Annotation: It should be noted that the effect of bosentan on the prevention of new DUs in SSc has not been proven for other ERA. The results of two double-blind RCTs (DUAL-1 and DUAL-2), which were published after closure of literature research deadline, did not show a significant difference between macitentan, a selective antagonist of endothelin-1 (ET-1) receptors, and placebo in prevention of new DUs over 16 weeks in patients with SSc with active DUs at baseline.\(^{42}\)

III. SSc-related PAH

Recommendation: ERA, PDE-5 inhibitors or riociguat should be considered to treat SSc-PAH (strength of recommendation: B extrapolation from RCTs including patients with SSc/CTD).

High-quality RCTs involving patients with different forms of PAH, including CTD-related PAH, indicate that endothelin antagonists (bosentan, ambrisentan and macitentan) improve exercise capacity and time to clinical worsening in patients with PAH.\(^{41-45}\) Adverse events associated with ERA treatment in these clinical trials included abnormal liver function tests, peripheral oedema, palpitations, headache, chest pain, nasal congestion and anaemia, but the safety profile differed for specific agents.\(^{45}\)

Sitaxentan, a selective ERA which was included in the 2009 EULAR recommendations for the treatment of SSc, has been
withdrawn from the market in December 2010 due to its hepatotoxicity.2 44

High-quality RCTs involving heterogeneous patients with PAH, including CTD-PAH, indicate that selective PDE-5 inhibitors (sildenafil and tadalafil) improve exercise capacity in patients with PAH and (tadalafil 40 mg/day) reduce risk of clinical worsening (reviewed in refs. 44 and 45). The most common side effects associated with PDE-5 inhibitors included flushing, dyspepsia, diarhoea, headache and myalgia.

Another RCT including patients with different forms of PAH, including patients with CTD-PAH, showed that riociguat, a soluble guanylate cyclase stimulator, improves exercise capacity, time to clinical worsening and haemodynamic parameters in patients with PAH.46 Drug-related serious adverse events included syncope, increased hepatic enzyme levels, dizziness, acute renal failure and hypotension.46

Based on the results of these high-quality RCTs, ERAs (bosentan, ambrisentan and macitentan), selective PDE-5 inhibitors (sildenafil and tadalafil) and riociguat have been approved for treatment of PAH associated with CTDs.44 47 48 The evidence regarding usage of these drugs specifically in SSc-PAH is less robust.

Experts recommend that ERA, selective PDE-5 inhibitors and riociguat should be considered in the treatment of SSc-PAH in agreement with international guidelines regarding treatment of PAH.44 This has been underlined by the publication of the recently published new guidelines of the pulmonology and cardiology societies.49

In severe or progressing PAH cases combination therapy with different PAH-specific drugs should be taken into account. Although at the time of developing these recommendations RCTs comparing combination therapy with PAH-specific drugs versus monotherapy in patients with SSc-PAH were lacking, this approach is in line with recent guidelines of the European cardiology and pulmonology societies regarding management of PAH in general, and seems particularly important in patients with SSc-PAH known to have more progressive disease than patients with other forms of PAH.49

Recommendation: Intravenous epoprostenol should be considered for the treatment of patients with severe SSc-PAH (class III and IV) (strength of recommendation: A).

Prostacyclin analogues should be considered for the treatment of patients with SSc-PAH (strength of recommendation: B: extrapolation from RCTs including patients with SSc/CTD).

One RCT (Jadad score 3), involving 111 patients with SSc-PAH, showed that epoprostenol (continuous intravenous infusion, starting dose 2 ng/kg/min and increased based on clinical symptoms and tolerability) in combination with conventional therapy (diuretics, oral anticoagulants, oxygen and glycosides), improves exercise capacity, functional status and haemodynamic measures in SSc-PAH, compared with conventional therapy.50 The median 6 minute walk test (6MWT) distance improved by 108 m (95% CI 35 to 180; p=0.001; epoprostenol vs control group), the New York Heart Association (NYHA) functional class improved in 21 (38%) patients treated with epoprostenol and none in the control group (number needed to treat (NNT) 2.7) and the Borg dyspnoea index and the dyspnoea fatigue score also improved significantly. The beneficial haemodynamic effects of epoprostenol included a statistically significant decrease in pulmonary vascular resistance, mean pulmonary artery pressure and right atrial pressure, as well as a significant increase in cardiac index.50

Based on the results of the RCT and two large long-term observational studies, which have documented an improvement in survival of patients with idiopathic PAH treated with epoprostenol, intravenous epoprostenol has been approved by the Food and Drug Administration (FDA) for the treatment of severe (WHO class III or IV) PAH.44 45 51 52

As a result of a very short half-life, epoprostenol is administered through a permanent indwelling central venous catheter, which may incite adverse events: infections, pneumothorax and haemorrhage.53 Sudden disruption/withdrawal of intravenous epoprostenol (due to catheter/vein thrombosis and/or patient’s decision) may lead to life-threatening PAH rebound. Based on overall risk-to-benefit considerations, and in agreement with the current guidelines, experts recommend intravenous epoprostenol as the treatment of choice in severe, therapy-resistant SSc-PAH, which are in line with those of recently published guidelines of other societies.44 49

Based on the results of high-quality RCTs involving patients with different forms of PAH, including patients with CTD-PAH, other prostacyclin analogues such as treprostinil (intravenous, subcutaneous or inhaled) and iloprost (inhaled), have been approved for treatment of PAH, including PAH associated with CTD.44 45 Side effects associated with usage of intravenous treprostinil are similar to that reported with intravenous epoprostenol and include headache, jaw pain, diarhoea, abdominal pain, anorexia, vomiting, photosensitivity, cutaneous flushing and arthralgias, as well as the risk of complications associated with continuous infusion via catheter. Subcutaneous infusion of prostanoids is frequently associated with pain at the infusion site. Inhaled prostanoids can result in cough, headache, flushing, nausea and syncope.55

Despite the lack of specific RCTs evaluating these drugs exclusively in patients with SSc, experts recommend that these prostacyclin analogues should be considered for treatment of SSc-PAH, in agreement with international guidelines for PAH treatment.44 49

The experts concluded that combining different classes of PAH-specific therapies may be considered in the treatment of selected patients with SSc-PAH, especially in those with severe or progressing disease. As discussed in previous paragraph, this approach is in line with recently published guidelines regarding management of PAH in general, and seems particularly important in patients with SSc-PAH known to have more progressive disease than patients with other forms of PAH.49

IV. Skin and lung disease

Recommendation: Methotrexate may be considered for treatment of skin manifestations of early diffuse SSc (strength of recommendation: A).

In one RCT (Jadad score 3), involving 29 patients with diffuse SSc or limited SSc (mean duration of skin involvement 3.2 years), methotrexate (intramuscularly at a dose of 15 mg/week for 24 weeks) showed a trend towards improvement of the total skin score (p=0.06 vs placebo).34

In the second RCT (Jadad score 5), involving 73 patients with early diffuse SSc, methotrexate, given orally at a dose of 10 mg per week for 12 months, decreased the University of California Los Angeles (UCLA) skin score (ES 0.5, 95% CI 0.0 to 1.0) and the modified Rodnan skin score (mRSS, ES 0.5; 95% CI 0.0 to 0.9) compared with placebo in an intention-to-treat analysis.65 A beneficial effect of methotrexate (over placebo) on skin manifestations has been confirmed by a reanalysis of the trial by Pope et al.65 which, using a Bayesian methodology, showed that the probability that methotrexate improves mRSS and the UCLA skin score were 94% and 96%, respectively.66 No significant effects on other organ

manifestations were shown. In the study evaluating patients with early diffuse systemic sclerosis (dSSc), 11 out of 36 patients (31%) in the placebo group and 12 out of 35 patients (34%) in the methotrexate group dropped out before study completion, mainly due to treatment inefficacy. There were few premature discontinuations due to adverse events (number needed to harm 16 and 34.5 in both RCT, respectively). There were no significant differences in the mortality rate (3 vs 7.3, p=0.18), although the trend was in favour of methotrexate. Safety concerns associated with methotrexate include liver toxicity, pancytopenia, its potential teratogenicity and, possibly, the induction of lung injury. It should be noted that in both RCTs evaluating methotrexate in SSc, relatively low dose of methotrexate was used. Whether higher doses of methotrexate, which are used in treatment of rheumatoid arthritis and other inflammatory diseases, could increase treatment effectiveness without significant increase in risk of side effects remains to be established. In paediatric patients, methotrexate dose of 25 mg/m² weekly orally or subcutaneously is well tolerated.

Thus, the experts confirmed the earlier recommendation for methotrexate in early diffuse SSc.

It should be recognised that cyclophosphamide (CYC) has also been shown, in RCTs, to improve skin changes in patients with SSc, and other agents such as mycophenolate mofetil or azathioprine are used to treat skin involvement, although their efficacy has not been studied extensively. The evidence regarding efficacy of CYC in SSc-ILD results mainly from two high-quality (Jadad score 5) RCTs and their subanalyses. The first trial (Scleroderma Lung Study, SLS), involving 158 patients with SSc with active alveolitis, demonstrated that CYC given orally at a dose of 1–2 mg/kg per day improved lung volumes, dyspnoea score and quality of life over 12 months compared with placebo. The placebo-corrected mean (95% CI) improvement in forced vital capacity (FVC) and total lung capacity (TLC) was 2.5% (0.3% to 4.8%) and 4.1% (0.5% to 7.7%), respectively (p=0.03 for both measures). No significant effect on diffusing lung capacity for carbon monoxide (DLCO) could be demonstrated. CYC also improved the transitional dyspnoea index, the health assessment questionnaire (HAQ) disability index, and the vitality and health-transition domains of the Short-Form 36 (p<0.05 vs placebo for all measures). Subanalysis of the SLS revealed that CYC therapy was also associated with significant improvement in high resolution computed tomography (HRCT) score. Extension of the SLS study showed that the FVC continued to improve after cessation of CYC treatment reaching a maximum at 18 months: 6 months after stopping CYC therapy (mean FVC difference vs placebo: 4.16%, p=0.01). The beneficial effects of CYC disappeared 1 year after CYC was terminated. The effect of CYC was greater in patients with more severe lung and/or skin disease. The mean FVC improvement in patients with baseline FVC lower than 70% of predicted was 4.62% at 12 months and 6.8% at 18 months (p<0.006 for both time points), while in patients with baseline FVC >70% of predicted, the mean treatment effect was 0.55% at 12 months and 2.67% at 18 months (p>0.05 for both time points). Another subanalysis of the SLS study revealed that the HRCT score and skin disease were independent predictors of response to CYC therapy. In patients with 50% or more of any lung zone involved by reticular infiltrates on HRCT and/or with mRSS of at least 23/51, the CYC treatment effect was 9.81% at 18 months (p<0.001) versus no treatment effect (0.58% difference, p>0.05) in patients with less severe HRCT findings and a lower mRSS at baseline.

The second trial evaluated CYC (intravenously at a dose of 600 mg/m²/month) compared with placebo in 43 patients with SSc with SSc-ILD. Active treatment included six infusions of CYC given at 4-week intervals followed by oral azathioprine (2.5 mg/kg/day) or placebo for 6 months. Prednisolone (20 mg on alternate days) was co-administered in the active treatment group. The mean adjusted between-group difference in FVC was 4.2% in favour of CYC, which just missed statistical significance (p=0.08). The lung diffusing capacity for carbon monoxide and other outcome measures did not improve.

Considering the results of both RCTs and the fact that the benefit of CYC was mainly due to inhibition of progression of SSc-ILD, experts recommend that CYC therapy should be considered in particular in patients with progressive lung disease. As in the previous 2009 recommendations there was unanimous consensus of the experts with respect to the CYC dose and duration of treatment to be tailored individually dependent on the clinical condition and response. Potential risks of bone marrow suppression, teratogenicity, gonadal failure and haemorrhagic cystitis must be always considered.

Recommendation: Haematopoietic stem cell transplantation (HSCT), should be considered for the treatment of selected patients with rapidly progressive SSc at risk of organ failure. In view of the high risk of treatment-related side effects and of early treatment-related mortality, careful selection of patients with SSc for this kind of treatment and the experience of the medical team are of key importance (strength of recommendation: A).

The results of two RCTs evaluating the efficacy and safety of high-dose immunosuppressive therapy with subsequent HSCT have been published so far. The first single-centre trial (Jadad 3), including 19 patients with SSc with mRSS>14 and internal organ involvement or mRSS<14 and SSc-ILD, showed that HSCT (200 mg/kg CYC and rabbit antithymocyte globulin 6.5 mg/kg intravenously in total, preceded by CYC 2 g/m² and filgrastim as part of the mobilisation step prior to leukapheresis) was superior to CYC (intravenously, 1 g/m²/month for 6 months) therapy with respect to improvement of skin score and lung volumes. No significant effect on diffusing capacity of the lungs for carbon monoxide could be demonstrated.

Another multicentre RCT (ASTIS) compared HSCT (200 mg/kg CYC and rabbit antithymocyte globulin 7.5 mg/kg intravenously in total, preceded by CYC 4 g/m² and filgrastim as part of the mobilisation step) with CYC pulse therapy (intravenously, 750 mg/m²/month for 12 months) in 156 patients with SSc with early diffuse SSc, mRSS≥15 and internal organ involvement or with an mRSS>20 without internal organ involvement. HSCT was associated with increased treatment-related mortality in the first year (eight deaths in HSCT group vs none in CYC group, p=0.007) but significantly improved long-term event-free survival (HR; 95% CI 0.52; 0.28 to 0.96, p=0.04 and 0.34; 0.16 to 0.74, p=0.006 at 1-year and 3-year through 10-year follow-up) and overall survival (HR; 95% CI 0.48; 0.23 to 0.91, p=0.02 and 0.29; 0.13 to 0.64, p=0.002 at 1-year and 3-year through 10-year follow-up). HSCT therapy resulted in significant improvement in the mRSS (mean difference; 95% CI 11.1; 7.3 to 15.0, p<0.001), FVC (mean difference; 95% CI 9.1; 14.7 to 2.5, p=0.004) and TLC (mean difference; 95% CI 6.4; 11.9 to 0.9, p=0.02) at 2 years’ follow-up. No significant effect on DLCO could be found. Mean change in creatinine clearance was significantly worse in the HSCT group than in the
control group (mean difference; 95% CI 10.9; 1.5 to 20.3, p=0.02). Causes of treatment-related deaths in HSCT included Epstein-Barr virus reactivation, lymphoma, heart failure, myocardial infarction and acute respiratory distress syndrome. HSCT therapy was also associated with higher risk of viral infections (27.8% in the HSCT group vs 1.3% in the control group, p<0.001).

In view of the results of the two RCTs and considering the risk of potential treatment-related mortality and morbidity experts recommend that HSCT should be considered for the treatment of selected patients with rapidly progressive SSc at risk of organ failure. To reduce the risk of treatment-related side effects, HSCT should be performed in selected centres with experience in this kind of treatment. Careful evaluation of the benefit to risk ratio in individual patients with SSc selected for HSCT should be done by experts. Further studies should help to identify subgroups of patients with SSc in whom HSCT would be most beneficial.

V. Scleroderma renal crisis

RCTs evaluating the efficacy of ACE inhibitors in the treatment of SRC are lacking. Since the first report demonstrating a beneficial effect of ACE inhibitors in two patients with SRC, numerous case reports and uncontrolled studies have reported on ACE inhibitors in SRC.66–72 A prospective analysis of 108 patients with SRC has suggested that patients on ACE inhibitors (captopril in 47 and enalapril in 8) had a significantly better survival rate at 1 year (76%) and 5 years (66%) compared with patients not on ACE inhibitors (15% at 1 year and 10% at 5 years, respectively). The beneficial effect of ACE inhibitors on survival in SRC remained significant after adjustment for age and blood pressure (p=0.001).68 Another prospective uncontrolled study of 145 patients with SRC treated with ACE inhibitors demonstrated survival rates at 5 and 8 years after the onset of SRC of 90% and 85%, respectively.69 Two more recent retrospective studies including 91 and 110 patients with SRC, respectively, the majority of whom (91% and 98%, respectively) were treated with ACE inhibitors and/or angiotensin receptor antagonists (ARA) reported survival rates from 71% to 82% at 1 year, 59% to 60% at 5 years and 42% to 47% at 10 years.71,72 In comparison, 3 out 7 (43%) patients without ACEI/ARA-2 died within the first months after SRC onset.71

It is highly unlikely that a formal RCT will be conducted in this rare condition with high mortality. Despite the lack of RCTs, experts recommend the use of ACE inhibitors in the treatment of SCR. Experts believe that an immediate start of high-dose ACE inhibitors in patients who develop SRC is of key importance for improving their outcome. ACE inhibitors should be continued long term as long as there is any chance for additional improvement in kidney function.

The experts decided also to highlight that published evidence does not support the preventive use of ACE inhibitors to decrease risk of development or improve outcome of SCR.70,71

Recommendation: Blood pressure and renal function should be carefully monitored in patients with SSc treated with glucocorticoids (Strength of recommendation: C).

Evidence regarding the impact of steroid use on the development of SRC comes mainly from retrospective studies most of which showed significant association between steroid exposure and the occurrence of SRC.67,70,71,74–77 A case–control analysis including 220 patients with SSc showed that 36% of patients with SRC had received prednisone at a dose of 15 mg/day or more within 6 months preceding the onset of SRC, compared with 12% matched controls (OR; 95% CI 4.4; 2.1 to 9.4; p<0.001).74

Another analysis of the main risk factors for SRC suggested that patients with a high skin score, joint contractures and prednisone use (10 mg/day in 9 out of 10 patients) were at a higher risk (43% vs 21% of patient without steroids) of SRC.75

In two more recent studies, including 518 and 410 patients with SSc, respectively, steroid use (adjusted OR; 95% CI 4.98; 1.52 to 16.3, p=0.008 and HR; 95% CI 1.105; 1.004 to 1.026, p=0.006, respectively) was an independent predictor of SRC.74,76 A risk to develop SRC increased by 1.5% for every mg of prednisone/day consumed the trimester prior SRC.76

A retrospective analysis including 140 patients with SRC showed that high doses of steroids (prednisone ≥30 mg/day) were used more frequently in patients with SSc with normoten- sive SRC (64%) as compared with those with hypertensive SCR (16%) suggesting an association between the use of high-dose steroids and the risk of normotensive SRC which is associated with worse prognosis.67

The experts recognise that glucocorticoids, which are used in SSc, are part of the therapeutic strategy in the management of ILD, diffuse cutaneous disease or musculoskeletal involvement, although the evidence regarding their efficacy in SSc is limited.78 Considering the potential risk of SRC associated with steroid use experts recommend that patients with SSc treated with steroids should be carefully monitored with respect to the development of SRC.

VI SSc-related GI disease
Recommendation: PPIs should be used for the treatment of SSc-related gastro-oesophageal reflux and prevention of oesophageal ulcers and strictures (strength of recommendation: C).

Large, specific RCT for the efficacy of PPI in patients with SSc are lacking. A small RCT indicated that PPI may improve upper GI symptoms in patients with SSc.79 The efficacy of PPI in the treatment of GERD in the general population is well documented in meta-analyses of RCTs.80–82

In asymptomatic patients with SSc, PPI should be used with caution since long-term therapy with PPIs might lead to nutritional deficiencies, possibly due to reduced intestinal absorption, or increased risk of infections.83–85

Recommendation: Prokinetic drugs should be used for the management of SSc-related symptomatic motility disturbances (dysphagia, GERD, early satiety, bloating, pseudo-obstruction, etc) (strength of recommendation: C).

Small RCTs involving patients with SSc or CTD indicate that the short-term usage of cisapride has a beneficial effect on gastric emptying and lower oesophageal sphincter pressures.90–92 However, in many countries, cisapride has either been withdrawn or has limited access as a result of reports about long QT syndrome caused by cisapride, which predisposes to severe arrhythmias.91

Long-term efficacy RCTs of other prokinetics in SSc were not found. Several non-randomised or uncontrolled studies suggest that prokinetics may improve GI signs and symptoms in patients with SSc.92–95

Several prokinetic drugs have shown beneficial effects in RCTs involving patients with other than SSc-related dysmotility disorders or are under evaluation (for review see refs. 96 and 97).

The experts conclude that all available prokinetic drugs can be applied to patients with SSc with GI involvement on an individual basis, in consideration of potential benefit to risk ratio. Whether these drugs would be effective in the treatment of...
SSc-related symptomatic motility disturbances in a general manner is at present only speculative and needs urgently to be investigated.

Recommendation: Intermittent or rotating antibiotics should be used to treat symptomatic small intestine bacterial overgrowth (SIBO) in patients with SSc (strength of recommendation: D).

Two small uncontrolled, non-randomised studies suggest that treatment with antibiotics might improve symptoms in patients with SSc with SIBO.98 99 No RCTs regarding the efficacy of antibiotics in the treatment of SSc-related bacterial overgrowth or malabsorption were found.

In general, treatment of symptomatic small intestinal bacterial overgrowth is based on empirical courses of one or more broad-spectrum antibiotics with activity against both aerobic and anaerobic enterobacteria such as quinolones, amoxicillin-clavulanic acid, metronidazole, neomycin or doxycycline. The principles of diagnosis and treatment strategies of this condition have been summarised in an excellent review.100

Internal evaluation of recommendations
All task force members took part in the online-based evaluation of the updated recommendations. The results of this evaluation are presented in table 1. All but one recommendation received mean scores of more than 7 indicating high level of agreement. The mean score for the recommendation regarding fluoxetine for the treatment of SSc-related RP was 6.06 which is consistent with medium level of agreement.

Research agenda
In addition to the recommendations, experts formulated a research agenda which addresses usage of pharmacological treatments in SSc or SSc-related organ complications which were considered of particular interest (box 1). This research agenda can be helpful in developing further clinical research in SSc.

DISCUSSION
As compared to the previous (2009) EULAR recommendations for treatment of SSc, the updated recommendations include several new treatments for specific SSc-related organ involvement. The greatest changes have been made in treatments of vascular complications of SSc and mirror the progress which had been made in this field during the last several years. These include the introduction of PDE-5 inhibitors for SSc-related RP and DUs, riociguat and new aspects for ERAs, prostacyclin analogues and PDE-5 inhibitors for SSc-PAH. The new recommendation regarding the use of fluoxetine for SSc-related RP was also added.

With regard to treatment of other than vascular complications of SSc, the recommendation for HSCT for selected patients with rapidly progressive SSc at risk of organ failure has been added.

Similar to the 2009 recommendations, the present recommendations address only pharmacological treatments which were considered most relevant and received consensus from the expert panel. As SSc is an uncommon and clinically heterogeneous disease, appropriate testing of therapies is difficult. Indeed, evidence supporting the present recommendations is often limited and some of the recommendations are supported by the evidence extrapolated from studies involving patients with diseases other than SSc or are based solely on expert opinion.

Similar to the 2009 recommendations, there is still not sufficient data, to make specific recommendation for paediatric patients. It would be important to have studies at least for the effective paediatric dose of each medication, to be safely applied.

It should be recognised that there are several other promising therapies, including immunosuppressive drugs or new biological agents which could not be included in the present recommendations because the evidence for their efficacy was considered insufficient at the time of developing these recommendations. The results of RCT evaluating new therapies in patients with SSc which were published after closure of the systematic literature research are presented in online supplementary table S4.

The first of these trials evaluated the efficacy of sildenafil in DUs healing in patients with SSc and is addressed in the comment following recommendation concerning treatment of DUs.109

Another double-blind, phase 2 RCT involved 87 patients with early diffuse SSc and elevated acute phase reactants. Treatment with tocilizumab (subcutaneous 162 mg/week) was associated with a favourable trends in skin score improvement as compared with placebo after 24 weeks (p=0.09) and 48 weeks (p=0.06). In addition, encouraging changes in FVC were noted. In view of promising effects of tocilizumab on skin and lung involvement, it is concluded that further studies are warranted before definitive conclusions can be made about its risks and benefits in SSc.101

The results of another RCT, the SLS 2 comparing mycophenolate moefit with CYC in patients with SSc-ILD are expected to be published soon. The preliminary results of this study, recently published as an abstract of the 2015 ACR annual congress, indicate that mycophenolate moefit (up to 3 g/day orally for 2 years) was comparable with oral CYC (2 mg/kg/day for 1 year followed by matching placebo for the second year) with regard to FVC course at 24th month.102 However, final conclusions regarding the place of mycophenolate moefit in the treatment of SSc-ILD cannot yet be made. Other therapies, considered promising by the experts, were addressed in the research agenda (box 1). Since ‘lack of evidence of efficacy’ does not imply that ‘efficacy is absent’ the absence of positive recommendation regarding specific drug should not be interpreted as a contraindication for its use.

It should also be emphasised that there are other treatment options, such as education, physiotherapy or local management of ischaemic lesions which were beyond the scope of the project or could not be included in the present recommendations due to lack of consensus among the experts.

In conclusion, it is believed that these updated recommendations will help to improve care of patients with SSc in an evidence-based way and indicate direction for further clinical research. Considering the significant complexity and heterogeneity of SSc and the limited evidence for treatments, it is recommended that patients with SSc should be referred to specialised centres with appropriate expertise in SSc management.

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