Update of EULAR recommendations for the treatment of systemic sclerosis

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ABSTRACT

Objectives: The aim was to update the 2009 EULAR recommendations for the treatment of systemic sclerosis (SSc), with attention to new therapeutic questions.

Methods: 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 USA, two patients nominated by the pan-European patient association for SSc (FESCA), a clinical epidemiologist and 2 research fellows. All centers from the EULAR Scleroderma Trials and Research (EUSTAR) group 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.

Results: The procedure resulted in sixteen 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.

Conclusions: These updated data- 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 tract and musculoskeletal system. Involvement of internal organs results in significant morbidity and mortality of SSc patients. Clinical complexity and heterogeneity of SSc leaves treatment of this disease very challenging.[1] Establishing the first EULAR recommendations for the treatment of SSc in 2009 was therefore a milestone for improving care of SSc patients 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 up-date of the 2009 EULAR recommendations has been recognized by the EULAR Scleroderma Trials and Research group (EUSTAR) and acknowledged by the European League against Rheumatism (EULAR). Following EULAR standardized 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 up-dated recommendations regarding pharmacological treatment of SSc-specific organ involvement were formulated. It should be recognized that the field of management of SSc patients 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 for 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 recognize 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.[2] 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). 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 3-round web-based Delphi exercise to members of EUSTAR centres, as previously described [6]. The Delphi exercise was completed until May 2014. For more details regarding the Delphi exercise please see the online supplement.

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 (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 September 30th, 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 September, 30th, 2014. A standardized search strategy was used for all clinical questions (online supplementary table S2). Medical subject heading (MeSH) search (exploded) was used for PubMed and a keyword search was

used for 2012-2014 or if the MeSH term was not available. For every clinical question, the publications found were screened for eligibility by reading title and abstract. The reference lists of meta-analyses, reviews or systematic reviews were examined to find additional studies.

For details regarding selection of studies, classifying and evaluation of evidence as well as data extraction see online Supplement.

Recommendations

The evidence of the individual studies was combined to achieve a recommendation in agreement with the GRADE system.[5, 12] Accordingly, an evidence profile and a summary of outcomes table were made for every clinical question by AK or MB. Using these results, a set of draft recommendations were prepared by OKB, JF, UML, YA and OD. The draft recommendations were sent to the expert panel in advance of the second face-to-face consensus meeting in October 2014. Draft recommendations were presented one-by-one together with the evidence profile and outcome tables, moderated by JF. Based on the nominal group technique, all recommendations were discussed, could be reformulated, and a level of evidence was attached, until consensus was reached among all participating experts.

RESULTS:

The procedure as described above resulted in sixteen recommendations being developed (instead of 14 in 2009). These recommendations 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. The final set of recommendations, grouped according to organ systems and the future research agenda are summarized in tables 1 and 2, respectively.

In addition to the main recommendations, the experts decided to formulate, several comments addressing therapeutic modalities in research questions, of which at present neither literature-based evidence nor clinical experience allowed precise recommendations to be made (Table S3 in online Supplement).

I. Raynaud phenomenon in SSc patients (SSc-RP)

1. A meta-analysis of RCTs on **dihydropiridine-type calcium antagonists** indicates that nifedipine reduces the frequency and severity of SSc-RP attacks. A meta-analysis of RCTs indicates that **PDE-5 inhibitors** reduce the frequency and severity of SSc-RP attacks. Dihydropiridine-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*. (strength of recommendation: A)*

One meta-analysis, including 8 randomized controlled trials (RCTs): seven with nifedipine and one with nicardipine, with 109 SSc patients involved, indicated that dihydropiridine-type calcium antagonists reduce the frequency and severity of ischaemic attacks in SSc-RP.[13-20] The weighted mean difference (WMD) of all

calcium antagonists versus placebo (six trials) for 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.[13]

Another meta-analysis of 6 RCTs (2 with sildenafil, 3 with tadalafil and 1 with vardenafil) including 236 patients with CTD-related Raynaud's phenomenon, of whom 95% were patients with SSc, showed that phosphodiesterase type 5 (PDE-5) inhibitors improve frequency, severity and duration of RP attacks.[21-27] The treatment effect (mean difference; 95% confidence interval (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, myalgias, 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 SSc patients with severe RP and/or those who do not satisfactorily respond to calcium channel blockers***.

2. A meta-analysis of RCTs on **prostanoids** indicates that intravenous iloprost reduces the frequency and severity of SSc-RP attacks. Intravenous iloprost should be considered for severe SSc-RP *(strength of recommendation: A).*

Experts recommend that i.v. 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 SSc patients in total, indicates that iloprost is effective in reducing the frequency and severity of SSc-RP.[28-35] Iloprost, given intravenously (0.5–3 ng/kg per minute 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 prostanoids 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.[34-38]

Two RCTs comparing intravenous iloprost (0.5–2 ng/kg per minute 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.[18, 39]

In view of costs and feasibility, the experts recommended that intravenous prostanoids 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 prostanoids are combined with other vasodilators.***

3. One small study indicates that **fluoxetine** might improve SSc-RP attacks. 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 (p.o. 20 mg/day) was superior to nifedipine LA (p.o. 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 SSc patients neither for fluoxetine nor for nifedipine, which could be due to the low number of SSc patients 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 recognize that fluoxetine*** is used in practice and ***believe that fluoxetine is a useful alternative for treatment of SSc-related RP***, in particular in SSc patients who cannot tolerate or do not respond to vasodilators.

Since the data regarding the use of fluoxetine in SSc patients 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

[https://www.medicines.org.uk/emc/medicine/25737]. Of note, withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt.

II. Digital ulcers in SSc patients

4. Two RCTs indicate that **intravenous iloprost** is efficacious in healing digital ulcers in patients with SSc. Intravenous iloprost should be considered in the treatment of digital ulcers in patients with SSc. *(strength of recommendation: A)*

Intravenous iloprost (0.5–2 ng/kg per minute 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 SSc patients with active DUs (p=0.06 vs placebo for 50% improvement).[32-33] 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.[18, 39]

One meta-analysis published in 2013 included, in addition to the 2 abovementioned RCTs with intravenous iloprost, 2 additional RCTs, one with oral iloprost (100 µg/day or 200 µg/day versus placebo for 6 weeks) and one with oral treprostinil (slow release up to 16 mg bid for 20 weeks).[37, 41] This analysis revealed a trend towards a beneficial effect of prostanoids 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).[42] 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 summarizing the effect of 4 RCTs (2 with iv 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).[42] Again, the greatest effect was seen with iv iloprost (RR; 95%CI: 1.18; 0.30 to 4.72). When the results of the small study by Wigley et al. were evaluated separately, they suggest that intravenous iloprost may prevent new DUs in SSc patients (standardized mean difference (SMD); 95%CI for number of DUs: -0.77; -1.46 to -0.08, p=0.03).[32, 42] Moreover, a RCT with epoprostenol, administered continuously for severe SSc-related pulmonary arterial hypertension (SSc-PAH), revealed a tendency towards a reduction in the number of new digital ulcers (by 50%).

Considering the fact that oral prostanoids showed lower efficacy for treatment of SSc-related Raynaud's phenomenon, as compared with iv iloprost (see section on RP), the ***experts decided***, based on the results of the above-mentioned 2 RCTs, ***to recommend intravenous iloprost as a treatment for DUs in SSc patients.*** Further studies are required to confirm beneficial effect of iv iloprost in prevention of development of DUs in SSc patients. In view of risk of side effects and route of administration usually requiring hospitalization, intravenous iloprost should be considered in particular in SSc patients with DUs not responding to oral therapy. In severe cases, combination therapy with oral vasodilator and i.v. iloprost can be used. However, the increased risk of side effects should be taken into account.

5. A meta-analysis of RCTs and results of an independent RCT indicate that **PDE-5 inhibitors** improve healing of digital ulcers in patients with SSc. Moreover, the results of one small RCT indicate that PDE-5 inhibitors may prevent development of

new digital ulcers in SSc. PDE-5 inhibitors should be considered in the treatment of digital ulcers in SSc patients. *(strength of recommendation: A)*

One meta-analysis of 3 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 SSc patients with Raynaud's phenomenon of whom 39 had baseline DUs indicated that selective PDE-5 inhibitors improve healing of DUs in SSc patients.[42] Although DUs healing was a co-primary outcome only in 1 of 3 RCTs included into the meta-analysis, and all 3 RCTs were underpowered to detect difference between active treatment and placebo, the pooled effect shows significant benefit of PDE-5 inhibitors over placebo on DUs healing.[23, 42] Both, the number of patients with DUs healing and the number of patients with DUs 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 DUs healing and 4.29; 1.73 to 10.66, $p<0.002$ for DUs improvement, respectively).[42] The results of this meta-analysis are corroborated by an independent multicentre RCT evaluating the effect of tadalafil (20 mg/d on alternate day for 8 weeks as an add-on-therapy to previous vasodilators) on DUs healing, as one of two co-primary end-points together with effect on Raynaud's phenomenon, in 31 SSc patients with baseline DUs.[26] After 8 weeks of treatment, DUs healed completely in 14 out of 18 patients in the tadalafil group as compared to 5 out of 13 patients in the placebo arm ($p<0.05$). The results of this study including altogether 53 SSc patients with SSc-related Raynaud's phenomenon 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 to 9 out of 26 patients from the placebo group ($p<0.05$). Tadalafil (20 mg/d

on alternate day for 6 weeks with one 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 SSc patients with secondary RP, 23 (95%) of whom had SSc, cited in the meta-analysis by Tingey at al.[25, 42] In this study, only 1 new DU developed under tadalafil treatment as compared with 13 new DUs which developed in 6 patients under placebo treatment ($p<0.05$).

Side effects of PDE-5 inhibitors are discussed in the previous paragraph regarding PDE-5 inhibitors in treatment of Raynaud's phenomenon.

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 SSc patients 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 DUs healing, in part due to unexpectedly high healing rates in placebo group.[43] 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 abovementioned meta-analysis by Tingey et al., the results of this study, which was published after data closure for the recommendations, did not change the respective recommendation [42-43].

6. **Bosentan** has confirmed efficacy in two high-quality RCTs to reduce the number of new digital ulcers in SSc patients. 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. *(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 SSc patients with a history of or at least one active DU 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 RAPIDS1 or 20 weeks in RAPIDS2, significantly reduced the number of new DUs in both trials.[44, 45] In a recent meta-analysis of RAPIDS1 and RAPIDS2, treatment with bosentan was associated with a significant reduction in the mean number of DUs per patient in the overall trials population (SMD; 95% CI: -0.34; -0.57 to -0.11, p=0.004) and in SSc patients with baseline DUs (SMD; 95% CI: -0.36; -0.61 to -0.11, p=0.005).[42] The effect of bosentan was most pronounced in SSc patients with multiple (4 or more) DUs at baseline (ES; 95%CI: -0.52; -1.01 to -0.02) as compared with SSc patients with lower number of DUs at baseline (ES; 95%CI: -0.08; -0.44 to 0.28) in RAPIDS2.[45]

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.[44-45]

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 DUs 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 trail [44-45]. Because of these data, the experts decided that in the present recommendations bosentan should be considered for reduction of new DUs in all SSc patients with DUs, 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 macicentan, a selective antagonist of ET-1 receptors, and placebo in prevention of new DUs over 16 weeks in SSc patients with active DUS at baseline [Khanna D 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]

III. SSc-PAH

7. Based on the results of high-quality RCTs including heterogeneous population of PAH patients, including CTD-PAH, several **ERA** (ambrisentan, bosentan, and macitentan), **PDE-5 inhibitors** (sildenafil, tadalafil) and **riociguat** have been approved for treatment of PAH associated with connective tissue diseases, ERA, PDE-5 inhibitors or riociguat should be considered to treat SSc-related PAH. *(strength of recommendation: B extrapolation from RCTs including SSc/CTD patients)*

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.[46-48] 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.[48]

Sitaxentan, a selective endothelin receptor antagonist 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, 47]

High quality RCTs involving heterogeneous PAH patients, 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 ref 47 and 48).[47-48] The most common side effects

associated with PDE-5 inhibitors included flushing, dyspepsia, diarrhoea, headache, and myalgia.

Another RCT including patients with different forms of PAH, including CTD-PAH patients, showed that riociguat, a soluble guanylate cyclase stimulator, improves exercise capacity, time to clinical worsening and hemodynamic parameters in PAH patients.[49] Drug-related serious adverse events included syncope, increased hepatic enzyme levels, dizziness, acute renal failure, and hypotension.[49]

Based on the results of these high quality RCTs, endothelin receptor antagonists (bosentan, ambrisentan, and macitentan), selective PDE-5 inhibitors (sildenafil, and tadalafil) and riociguat have been approved for treatment of PAH associated with connective tissue diseases.[47, 50-51] The evidence regarding usage of these drugs specifically in SSc-related PAH is less robust.

Experts recommend that ERA, selective PDE-5 inhibitors and riociguat should be considered in the treatment of SSc-related PAH in agreement with international guidelines regarding treatment of PAH.[47] This has been underlined by the publication of the recently published new guidelines of the pulmonology societies.[52]

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 SSc-PAH patients 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 SSc-PAH patients known to have more progressive disease that patients with other forms of PAH.[52]

8. One high-quality RCT in SSc patients indicates that continuous **intravenous epoprostenol** improves exercise capacity, functional class and haemodynamic measures in SSc-PAH. Intravenous epoprostenol should be considered for the treatment of patients with severe SSc-PAH (class III and IV). (*strength of recommendation*: A)

Based on the results of high-quality RCTs including heterogeneous PAH patients, including CTD-PAH, **other prostacyclin analogues (iloprost, treprostinil)** have also been registered for treatment of PAH associated with connective tissue diseases. Prostacyclin analogues should be considered for the treatment of patients with SSc-PAH. *(strength of recommendation: B: extrapolation from RCTs including SSc/CTD patients)*

One RCT (Jadad score 3), involving 111 SSc-PAH patients, showed that epoprostenol (continuous intravenous infusion, starting dose 2 ng/kg per minute 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.[53] The median 6MWT distance improved by 108 m (95% CI 55m to 180m; p=0.001; epoprostenol vs control group), NYHA functional class improved in 21 (38%) patients treated with epoprostenol and none in the control group (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.[53]

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 FDA for the treatment of severe (WHO class III or IV) PAH.[47-48, 54-55].

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.[56] 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***.[47, 52]

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.[47-48] Side effects associated with usage of iv treprostinil are similar to that reported with iv epoprostenol and include headache, jaw pain, diarrhoea, 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 [48].

Despite the lack of specific RCTs evaluating these drugs exclusively in SSc patients, experts recommend that these prostacyclin analogues should be considered for treatment of SSc-PAH, in agreement with international guidelines for PAH treatment.[47, 52]

The experts concluded that combining different classes of PAH-specific therapies may be considered in the treatment of selected SSc-PAH patients, 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 SSc-PAH patients known to have more progressive disease that patients with other forms of PAH.[52]

IV. Skin and lung disease

9. Two RCTs and their re-analysis have shown that **methotrexate** improves skin score in early diffuse SSc. Positive effects on other organ manifestations have not been established. 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 SSc 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).[57]

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.[58] A beneficial effect of methotrexate (over placebo) on skin manifestations has been confirmed by a re-analysis of the trial by Pope et al. which, using a Bayesian methodology, showed that the probability that methotrexate improves mRSS and the UCLA skin score were 94% and 96%, respectively.[58-59] No significant effects on other organ manifestations were shown. In the study evaluating early dSSc patients, eleven 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 (three vs seven; p=0.18), although the trend was in favour of methotrexate.[58] Safety concerns associated with methotrexate include liver toxicity, pancytopenia, its potential teratogenicity and, possibly, the induction of lung injury.[60] 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/week p.o. or s.c is well tolerated.

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

It should be recognized that cyclophosphamide (CYC) has also been shown, in RCTs, to improve skin changes in SSc patients, and other agents such as

mycophenolate mofetil or azathioprine are used to treat skin involvement, although their efficacy has not been studied extensively.[61]

10. 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 SSc patients with progressive ILD. *(Strength of recommendation: A)*

The evidence regarding efficacy of CYC in SSc-related interstitial lung disease (SS-ILD) results mainly from two high quality (Jadad score 5) RCTs and their sub-analyses.[61-62] The first trial (Scleroderma Lung Study, SLS), involving 158 SSc patients 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.[61] 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. Cyclophosphamide also improved the transitional dyspnoea index, the HAQ disability index, and the vitality and health-transition domains of the Short-Form 36 ($p<0.05$ vs placebo for all measures).[61] Sub-analysis of the SLS revealed that CYC therapy was also associated with significant improvement in HRCT score.[63] 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 versus placebo: 4,16%, p=0.01).[64] The beneficial effects of CYC disappeared one year after CYC was terminated. The

effect of CYC was greater in patients with more severe lung and/or skin disease.[64-65] 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% 18 months ($p> 0.05$ for both time points). Another sub-analysis of the SLS study revealed that the HRCT score and skin disease were independent predictors of response to CYC therapy.[65] 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 per month) compared with placebo in 45 SSc patients with SSc-ILD.[62] Active treatment included six infusions of CYC given at 4-week intervals followed by oral azathioprine (2.5 mg/kg per 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 forced vital capacity 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.[62]

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.[66]

11. Regarding **haematopoietic stem cell transplantation (HSCT)**, two RCTs have shown improvement of skin involvement and stabilization of lung function in SSc patients and one large RCT reports improvement in event-free survival in SSc patients as compared to cyclophosphamide in both trials. 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 SSc patients 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 haematopoietic stem cell transplantation (HSCT) have been published so far.[67, 68] The first single-centre trial (Jadad 3), including 19 SSc patients with mRSS >14 and internal organ involvement or mRSS<14 and SSc-ILD, showed that HSCT (200 mg/kg CYC and rabbit antithymocyte globulin 6.5mg/kg intravenously in total, preceded by CYC 2g/m2 and filgastrim as part of the mobilization step prior to leukapheresis) was superior to CYC (intravenously, 1g/m^2 per month for 6 months) therapy with respect to improvement of skin score and lung volumes.[67] 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 7.5mg/kg intravenously in total, preceded by CYC 4 g/m^2 and

filgrastim as part of the mobilization step) with CYC pulse therapy (intravenously, 750mg/m² per month for 12 months) in 156 SSc patients with early diffuse SSc, mRSS >/= 15 and internal organ involvement or with an mRSS > 20 without internal organ involvement.[68] HSCT was associated with increased treatment-related mortality in the first year (8 deaths in HSCT group versus none in CYC group, p=0.007) but significantly improved long-term event-free survival (HR; 95%CI: 0.52; 0.28-0.96, p=0.04 and 0.34; 0.16-0.74, p=0.006 at 1 and 3-through 10-year follow-up) and overall survival (HR; 95%CI: 0.48; 0.25-0.91, p=0.02 and 0.29; 0.13-0.64, p=0.002 at 1 and 3-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 SSc patients selected for

HRCT should be done by experts. Further studies should help to identify subgroups of SSc patients in whom HSCT would be most beneficial.

V. Scleroderma renal crisis (SRC)

12. Several cohort studies showed benefit in survival with use of ACE inhibitors in patients with SRC. Experts recommend immediate use of **ACE inhibitors** in the treatment of SRC. *(strength of recommendation: C)*

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.[69-75] A prospective analysis of 108 patients with SRC has suggested that patients on ACE inhibitors (captopril in 47 and enalapril in eight) 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).[71] 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.[72] 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.[74, 75]. In comparison, 3 out 7 (43%) patients without ACEI/ARA-2 died within the first months after SRC onset.[74]

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.[73-74, 76]

13. Several retrospective studies suggest that **glucocorticoids** are associated with a higher risk of SRC. Blood pressure and renal function should be carefully monitored in SSc patients 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.[70, 73-74, 77-80]

A case–control analysis including 220 SSc patients 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 (odds ratio; 95% CI: 4.4; 2.1 to 9.4; $p<0.001$).[77]

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 nine out of 10 patients) were at higher risk (43% versus 21% of patient without steroids) of SRC.[78]

In two more recent studies, including 518 and 410 SSc patients, respectively, steroid use (adjusted odd ratio; 95% CI: 4.98; 1.52 to 16.3, p=0.008 and hazard ratio; 95%CI: 1.105; 1.004 to 1.026, p=0.006, respectively) was an independent predictor of SRC.[74, 79] A risk to develop SRC increased by 1.5% for every mg of prednisone/day consumed the trimester prior SRC.[79]

A retrospective analysis including 140 patients with SRC showed that high doses of steroids (prednisone >/= 30 mg/day) were used more frequently in SSc patients with normotensive 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.[70]

The experts recognize 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 is SSc is limited [Iudici M et al. Clin Rheumatol. 2014;33:153-64]. Considering the potential risk of SRC associated with steroid use ***experts recommend that SSc patients treated with steroids should be carefully monitored with respect to the development of SRC.***

VI. SSc-related gastrointestinal disease

14. Despite the lack of large, specific RCT, ***experts recommend that PPIs should be used for the treatment of SSc-related gastroesophageal reflux and prevention of oesophageal ulcers and strictures*** *(strength of recommendation: B).*

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 SSc patients.[81] The efficacy of PPI in the treatment of GERD in the general population is well documented in meta-analyses of RCTs.[82-84]

In asymptomatic SSc patients, 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.[85-87]

15. Despite the lack of RCTs in SSc patients, ***experts recommend that 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 SSc or CTD patients indicate that the short-term usage of cisapride has a beneficial effect on gastric emptying and lower oesophageal sphincter pressures.[88-92] 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.[93]

Long-term efficacy RCTs of other prokinetics in SSc were not found. Several non-randomized or uncontrolled studies suggest that prokinetics may improve gastrointestinal signs and symptoms in SSc patients.[94-97]

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 ref. 98 and 99).[98-99]

The experts conclude that all available prokinetic drugs can be applied to SSc patients 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.

16. Despite the lack of RCTs in SSc patients, experts ***recommend the use of intermittent or rotating antibiotics to treat symptomatic small intestine bacterial overgrowth in SSc patients***. *(strength of recommendation: D)*

Two small uncontrolled, non-randomized studies suggest that treatment with antibiotics might improve symptoms in SSc patients with small intestine bacterial overgrowth (SIBO).[100-101] 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 summarized in an excellent review.[102]

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.

Table 1. The updated EULAR recommendations for treatment of systemic sclerosis, according to the organ involvement, including strength of the recommendations and the results of internal evaluation within the task force group.

Organ involvement	Recommendation	Strength of recommendation	Results of internal evaluation
I. Raynaud phenomenon in SSc patients (SSc-RP)	A meta-analysis of RCTs on **dihydropiridine-type calcium antagonists** indicates that nifedipine reduces the frequency and severity of SSc-RP attacks. A meta-analysis of RCTs indicates that **PDE-5 inhibitors** reduce the frequency and severity of SSc-RP attacks. Dihydropiridine-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.	A	8.19
	A meta-analysis of RCTs on **prostanoids** indicates that intravenous iloprost reduces the frequency and severity of SSc-RP attacks. Intravenous iloprost should be considered for severe SSc-RP. Experts recommend that i.v. iloprost should be used for treatment of SSc-RP attacks after oral therapy.	A	8.29
	One small study indicates that **Fluoxetine** might improve SSc-RP attacks. Fluoxetine might be considered in treatment of SSc-RP attacks.	C	6.06

II. Digital ulcers in SSc patients	Two RCTs indicate that **intravenous iloprost** is efficacious in healing digital ulcers in patients with SSc. Intravenous iloprost should be considered in the treatment of digital ulcers in patients with SSc.	A	8.39
	A meta-analysis of RCTs and results of an independent RCT indicate that **PDE-5 inhibitors** improve healing of digital ulcers in patients with SSc. Moreover, the results of one small RCT indicate that PDE-5 inhibitors may prevent development of new digital ulcers in SSc. PDE-5 inhibitors should be considered in treatment of digital ulcers in SSc patients.	A	8.03
	Bosentan has confirmed efficacy in two high-quality RCTs to reduce the number of new digital ulcers in SSc patients. 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.	A	8.19
III. SSc-PAH	Based on the results of high-quality RCTs including heterogeneous population of PAH patients, including CTD-PAH, several ERA (ambrisentan, bosentan, and macitentan), PDE-5 inhibitors (sildenafil, tadalafil) and riociguat have been approved for treatment of PAH associated with connective tissue diseases. ERA, PDE-5 inhibitors or riociguat should be considered to treat SSc-related PAH.	B	8.32
	One high-quality RCT in SSc patients indicates that continuous **intravenous epoprostenol** improves exercise capacity, functional class and haemodynamic measures in SSc-PAH. Intravenous epoprostenol should be considered for the treatment of patients with severe SSc-PAH (class III and IV).	A	8.10
	Based on the results of high-quality RCTs including heterogeneous population of PAH patients, including CTD-PAH, **other prostacyclin analogues (iloprost, treprostinil)** have also been registered for treatment of PAH associated with connective tissue diseases. Prostacyclin analogues should be considered for the treatment of patients with SSc-PAH.	B	
IV. Skin and lung disease	Two RCTs and their re-analysis have shown that **methotrexate** improves skin score in early diffuse SSc. Positive effects on other organ manifestations have not been established. Methotrexate may be considered for treatment of skin manifestations of early diffuse SSc.	A	7.42
	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 SSc patients with progressive ILD.	A	7.84
	Regarding **haematopoietic stem cell transplantation (HSCT)**, two RCTs have shown improvement of skin involvement and	A	8.03

	stabilization of lung function in SSc patients and one large RCT reports improvement in event-free survival in SSc patients as compared to cyclophosphamide in both trials. 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 SSc patients for this kind of treatment and the experience of the medical team are of key importance.		
V. Scleroderma renal crisis (SRC)	Several cohort studies showed benefit in survival with use of ACE inhibitors in patients with SRC. Experts recommend immediate use of **ACE inhibitors** in the treatment of SRC.	C	8.52
	Several retrospective studies suggest that **glucocorticoids** are associated with a higher risk of SRC. Blood pressure and renal function should be carefully monitored in SSc patients treated with **glucocorticoids.**	C	8.10
VI. SSc-related gastrointestinal disease	Despite the lack of large, specific RCT, experts recommend that PPI should be used for the treatment of SSc-related gastroesophageal reflux and prevention of oesophageal ulcers and strictures	B	8.58
	Despite the lack of RCTs in SSc patients, experts recommend that **prokinetic drugs** should be used for the management of SSc-related symptomatic motility disturbances (dysphagia, GERD, early satiety, bloating, pseudo-obstruction, etc).	C	7.97
	Despite the lack of RCTs in SSc patients, experts recommend the use of intermittent or rotating **antibiotics** to treat symptomatic small intestine bacterial overgrowth in SSc patients.	D	8.10

For explanations of the abbreviations see the text

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- Table 2. This research agenda can be helpful in developing further clinical research in SSc.

Table 2. Research agenda

Research agenda

1. Evaluation of the efficacy and safety of cyclophosphamide in the treatment of early diffuse SSc

2. Evaluation of the efficacy and safety of mycophenolate mofetil 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-PAH

6. Evaluation of calcium antagonists in the treatment of digital ulcers in SSc

7. Evaluation of statins in the treatment of digital ulcers in SSc

8. Evaluation of the efficacy and safety of ACE inhibitors in the prevention of SRC

9. Evaluation of the efficacy of non-pharmacological treatments in SSc

For explanations of the abbreviations see the text

DISCUSSION

As compared with 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 Raynaud's phenomenon and digital ulcers, riociguat and new aspects for endothelin receptor antagonists, prostacyclin analogues and PDE-5 inhibitors for SSc-related PAH. The new recommendation regarding the use of fluoxetine for SSc-related Raynaud's phenomenon was also added.

With regard to treatment of other than vascular complications of SSc, the recommendation for haematopoietic stem cell transplantation (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 recognized 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 SSc patients which were published after closure of the systematic literature research are presented in table S4 in online Supplement.

The first of these trials evaluated the efficacy of sildenafil in DUs healing in SSc patients and is addressed in the comment following recommendation concerning treatment of DUs.[43]

Another double-blind, phase 2 RCT involved 87 SSc patients with early diffuse SSc and elevated acute phase reactants. Treatment with tocilizumab (s.c. 162 mg per 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. [103]

The results of another RCT, the Scleroderma Lung Study 2 comparing mycophenolate mofetil with CYC in patients with SSc-related 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 mofetil (up to 3 g/day orally for 2 years) was comparable with oral CYC (2 mg/kg/day for one year followed by matching placebo for the second year) with regard to FVC course at 24th months.[104] However, final conclusions regarding the place of mycophenolate mofetil in the treatment of SSc-related ILD cannot yet be made. Other therapies, considered promising by the experts, were addressed in the research agenda (Table 2). 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 emphasized that there are other treatment options, such as education, physiotherapy or local management of ischemic 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 SSc patients 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 SSc patients should be referred to specialized centres with appropriate expertise in SSc management.

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The authors as listed on the title page of the manuscript have all made substantial contributions which qualifies them as authors. All authors have finally approved the submitted version to be published.

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