EULAR recommendations for the treatment of systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group (EUSTAR)

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Abstract

PURPOSE: Optimal treatment of systemic sclerosis (SSc) is a challenge because the pathogenesis of SSc is unclear and it is an uncommon and clinically heterogeneous disease affecting multiple organ systems. The aim of the EUSTAR (EULAR Scleroderma Trials and Research) group was to develop evidence-based, consensus-derived recommendations for the treatment of SSc.

METHODS: To obtain and maintain a high level of intrinsic quality and comparability of this approach, EULAR standard operating procedures were followed. The task force comprised 18 SSc experts from Europe, United States and Japan, 2 SSc patients and 3 fellows for literature research. The preliminary set of research questions concerning SSc treatment was provided by 74 EUSTAR centers.

RESULTS: Based on discussion of the clinical research evidence from published literature, and combining this with current expert opinion and clinical experience, 14 recommendations for the treatment of SSc were formulated. The final set includes the following recommendations: 3 on SSc-related digital vasculopathy (Raynaud’s phenomenon and ulcers), 4 on SSc-related pulmonary arterial hypertension, 3 on SSc-related gastrointestinal involvement, 2 on scleroderma renal crisis, 1 on SSc-related interstitial lung disease and 1 on skin involvement. Experts also formulated several questions for a future research agenda.

CONCLUSIONS: Evidence-based, consensus-derived recommendations are useful for rheumatologists to help guide treatment for patients with SSc. These recommendations may also help to define directions for future clinical research in SSc.
Introduction

Systemic sclerosis (SSc, scleroderma) affects the skin and multiple internal organs leading, eventually, to fibrosis [1]. The European League against Rheumatism (EULAR) and the EULAR Scleroderma Trials and Research (EUSTAR) group have acknowledged the need for evidence-based recommendations to be used in clinical practice. Following EULAR’s standard operating procedures, an ad hoc expert committee was established by EULAR and EUSTAR [2].

The present recommendations discuss the drug treatments, based on a combination of evidence and consensus, which, in the opinion of the community of SSc specialists (EUSTAR members and invited experts), were considered most important in the therapy of SSc. The appropriate management of SSc patients is complex and includes issues such as early diagnosis of internal organ involvement, identification of patients who are at risk of progressive disease, and non-pharmacological treatments, all of which are beyond the scope of this paper. Moreover, there are new promising therapies, as well as some established treatments, which have not yet been studied extensively enough to be included in the present set of recommendations but might be helpful in individual SSc patients. Some of these treatments are included in a comment section or research agenda. Thus, the absence of a positive recommendation cannot be taken as a recommendation against use or that the agent is proven to be unhelpful/dangerous.

The main aim of these recommendations is to provide guidance to rheumatologists and practitioners to approach and choose the treatment for SSc patients. No recommendations regarding contra-indications or what should NOT be done are included for procedural and other reasons.

Likewise, cost considerations, despite their importance, were not included in these considerations, as costs vary widely across countries and no uniform base case cost could be derived.

These recommendations are not meant to replace the physician’s clinical judgment. They should be viewed in terms of the clinician’s understanding of the individual patient and the clinician’s judgment of the balance between efficacy and toxicity of a treatment for a specific person. Although some treatment-related toxicities are mentioned in the text of recommendations or in the following comments, this 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.

Throughout this manuscript, the specific recommendation is followed by the evidence supporting the recommendation. It should be realized that the Committee utilized the evidence in each case and when evidence was not sufficient, supplemented it by the consensus-derived expert opinion to arrive at specific recommendations.

Consistent with EULAR guidelines for the generation of recommendations, only data up to a defined time point (December 2006) are included in the analysis. If new data become available later, they will be included in the next update which is also a regular feature of EULAR recommendations.

Methods

To obtain and maintain a high level of intrinsic quality and comparability, EULAR standardised operating procedures were followed [2]. The detailed methodology for developing EULAR/EUSTAR recommendations on the treatment of SSc has been previously reported [3]. Briefly, the task force included 18 SSc experts from Europe (two of them pediatric rheumatologists), the United States and Japan, 2 SSc patients from the Federation of
the European Scleroderma Associations (FESCA) and 3 fellows for literature research. The preliminary set of research questions concerning SSc treatment was provided by 74 EUSTAR centers. After a process of aggregation and data reduction by a modified Delphi technique, the experts selected the final set of 26 questions for the systematic literature research. Retrieved clinical trial publications were evaluated using the Jadad classification [4], and the level of evidence was graded from Ia to IV[5]. Outcome data for efficacy and adverse events were abstracted and effect size, number needed to treat (NNT) and number needed to harm (NNH) were calculated when appropriate.

Results
Evidence based approach
Out of 5421 publications identified, 281 were included in the final analysis. The methodology, including selection of research questions and literature search strategy, and the results of systematic literature research are presented separately [3].

Experts’ opinion approach
The final set of recommendations, grouped according to organ systems, and the future research agenda are summarized in Tables 1 and 2, respectively. The evidence that there are few high quality trials in SSc prompted the experts to also include information concerning the highest level of evidence based upon which a particular recommendation was formulated. Moreover, the experts decided to formulate, in addition to the main recommendations, several comments concerning medications or therapies addressed in research questions, on which at present neither literature-based evidence nor clinical experience allowed to make precise recommendation – Table 3. All recommendations and appropriate comments were accepted unanimously.

Final recommendations (propositions)

I. SSc-related digital vasculopathy (Raynaud’s phenomenon, digital ulcers)

1. A meta-analysis on dihydropiridine-type calcium channel blockers (CCBs) and one meta-analysis on prostanoids indicate that nifedipine and i.v. iloprost reduce the frequency and severity of SSc-related Raynaud’s phenomenon (RP) attacks. Dihydropiridine-type CCBs, usually oral nifedipine, should be considered for first-line therapy for SSc-related RP, and intravenous iloprost, or other available i.v. prostanoids, should be considered for severe SSc-related RP.

One meta-analysis, including 8 RCTs (7 with nifedipine and 1 with nicardipine, ref. 6-13) with 109 SSc patients involved, indicates that dihydropiridine-type CCBs reduce the frequency and severity of ischemic attacks in SSc-related RP [14]. The weighted mean difference (WMD) of all CCBs versus placebo (6 trials) for the reduction in the number of ischemic attacks over a 2-week period was 8.3 (95% CI: 0.9; 15.7). When 5 RCTs evaluating nifedipine (10-20 mg 3 times daily) versus placebo were analyzed separately, the reduction was greater with a WMD of 10.2 (95% CI: 0.3; 20.1).

The standardized mean difference (SMD) of all CCBs versus placebo (3 trials) for the reduction in the severity of ischemic attacks was 0.7 [95% CI 0.2; 1.2]. Clinically, this effect can be compared to a reduction in severity of 2.3 cm on a 10-cm visual analog scale (VAS), or more than 35% improvement as compared with placebo. Again, the effect of nifedipine alone versus placebo (2 trials) was greater (SMD [95%CI] 1.0 (0.2; 1.7).
Two randomized placebo-controlled trials in patients with mixed forms of RP evaluated the efficacy of diltiazem. These studies, which were not in the meta-analysis because they did not include an analysis on SSc patients only, gave contradictory results [15,16]. A second meta-analysis, that included the results of 5 RCTs with intravenous iloprost, one RCT with oral iloprost and one RCT with oral cisaprost, (ref. 17-23), with 332 SSc patients in total, indicates that iloprost is effective in reducing the frequency and severity of SSc-related RP [24]. Iloprost, given intravenously (0.5-3 ng/kg/min for 3 to 5 consecutive days sequentially) or orally (50ug to 150ug twice daily) significantly reduced the frequency of ischemic attacks, and improved the RP severity score in comparison with placebo (WMD [95%CI] 17.5 [15.7; 19.2]) and 0.7 [0.3; 1.1], respectively). Oral prostanoids seem to be generally less effective than intravenous iloprost in the treatment of SSc-related RP, although some beneficial effects could be seen with higher doses [17,19,24-27]. Two RCTs comparing intravenous iloprost (0.5-2 ng/kg/min for 3-5 days, every 6-8 weeks) with nifedipine (30-60mg/day) indicate that iloprost is only slightly superior to nifedipine in improving symptoms of SSc-related RP [10, 28].

In view of costs and feasibility, the experts recommended that CCBs are first-line therapy in the treatment of SSc-related RP. Intravenous prostanoids are recommended when CCBs have failed. It should be recognized that, in addition to CCBs and prostanoids, there are many other therapies which are in use for treatment of SSc-related Raynaud’s phenomenon – see on-line supplement. Since both types of drugs may induce side effects of vascular origin, the experts recommend particular attention if prostanoids are combined with CCBs.

2. Two RCT indicate that intravenous prostanoids (particularly i.v. iloprost) are efficacious in healing digital ulcers (DU) in patients with SSc. Intravenous prostanoids (in particular iloprost) should be considered in the treatment of active DU in patients with SSc.

Intravenous iloprost (0.5-2ng/kg/min for 3 to 5 consecutive days) significantly reduced the number of DU in comparison with placebo in one small RCT (Jadad score: 3), and improved DU healing in another RCT (Jadad score: 4) including 73 SSc patients with active DU (p=0.06 vs placebo for 50% improvement) [21-22]. In addition, two RCTs comparing intravenous iloprost with oral nifedipine suggest that both medications have a beneficial effect on DU healing, but the number of patients with DU in both trials was low [10,28]. Moreover, intravenous epoprostenol, administered continuously for severe SSc-related PAH, revealed a tendency towards a reduction of the number of new DU (by 50%) [29].

3. Bosentan has no proven efficacy in the treatment of active DU in SSc patients. Bosentan has proven efficacy in two high quality RCTs to prevent DU in diffuse SSc patients, in particular in those with multiple DU. Bosentan should be considered in diffuse SSc (dSSc) with multiple DU, after failure of CCBs and, usually, prostanoid therapy.

Bosentan, a dual endothelin receptor antagonist, was evaluated in two placebo-controlled RCTs (RAPIDS-1 and RAPIDS-2) (Jadad score: 5) involving 210 SSc patients in total [30-32]. Bosentan, at an oral dose of 62.5 mg twice daily for 4 weeks followed by 125 mg twice daily for another 12 weeks, significantly reduced the number of new DU by 48% as compared to placebo (ES [95%CI]: 0.4 [0.0; 0.8]) [31]. The efficacy of bosentan in preventing new DU formation was corroborated by the results of the recent RAPIDS-2 study, which was
performed in SSc patients with active DU (this is a population considered to be at high risk for peripheral digital necrosis) (mean placebo-adjusted improvement: 0.7 (39%) and 0.8 (30%) new ulcers per patient over 12 and 24 weeks respectively (p<0.05 vs placebo for both comparisons) [31-32]. Post-hoc subgroup analysis of RAPIDS-1 suggested that the highest effect of bosentan was found in dSSc (61% reduction over 16 weeks, p=0.0107 vs placebo), especially in dSSc with active DU (67%, p=0.0028 vs placebo), while in limited SSc (ISSc) the mean reduction was 38% when considering the entire population, and 30% if limited to patients with active DU [30]. It is anticipated that the results of RAPIDS-2, when published, will add new information concerning bosentan efficacy in the prevention of DU in SSc subsets.

Neither trial indicated that bosentan is superior to placebo in healing of SSc-related active DU, as evaluated by the time to complete- or partial healing of DU present at baseline, the time to healing of all DU, or the percentage of patients with complete DU healing (p>0.05 vs placebo for all comparisons) [30-32]. The beneficial effect on new DU formation was accompanied by a significant improvement in overall hand function (specific HAQ-score: ES [95%CI] 0.4 [0.0; 0.8]) in RAPIDS-1, and a significant improvement in the SHAQ dressing domain (p=0.03) in RAPIDS-2.

As discussed above, intravenous iloprost and epoprostenol were shown to improve healing of active DU [10, 21-22, 28-29]. CCBs, efficacious in the treatment of SSc-related RP, have been studied less extensively with respect to prevention and healing of DU in SSc. The results of two RCTs, with low numbers of patients with DU, suggest a comparable efficacy of CCBs and intravenous iloprost in healing active DU in SSc [10,28]. In a small RCT with 10 SSc patients nifedipine (30mg/day) reduced both the number of patients with new DU and the total number of new DU by 50% as compared with placebo over a 6-week period (NNT=3.3 for preventing new digital ulcers) [12]. The available evidence concerning CCBs and prostanoids in the prevention of new DU in SSc patients is far less comprehensive and robust than that of bosentan, but their toxicity pattern is milder, and long-term clinical experience suggests a good safety profile.

There are two major concerns related to the use of bosentan and other ERAs: potential liver injury and teratogenicity [33, 34]. Hormonal contraceptives may not be reliable if co-administered with bosentan, since bosentan may reduce their efficacy by interference with the cytochrome P450 system [35].

II. SSc-related pulmonary arterial hypertension

4. Two high quality RCTs indicate that bosentan improves exercise capacity, functional class and some hemodynamic measures in pulmonary arterial hypertension (PAH). Bosentan should be strongly considered to treat SSc-related PAH (SSc-PAH).

The efficacy of endothelin receptor antagonists (ERAs) in the treatment of PAH was analyzed in a meta-analysis of four RCTs evaluating bosentan and 1 RCT evaluating sitaxentan, (ref. 36-40) [see ref. 41 and online Supplementary material]. The results of this meta-analysis refer mainly to patients with idiopathic PAH (iPAH), who constituted the vast majority (mean: 67%, range: 53%-89%) of patients recruited in the analyzed studies. In SSc-PAH, known to have a worse prognosis than iPAH, only bosentan has been studied extensively including data concerning survival in SSc-PAH patients exclusively.

Two high quality (Jadad score: 5) placebo-controlled RCTs showed that bosentan (62.5mg twice daily during 4 weeks, followed by 125-250mg twice daily) significantly improved the 6MWT after 12 and 16 weeks in a heterogeneous population of PAH patients – Table 4 in online Supplementary material [36-37]. Improvement in exercise capacity coincided with an
improvement in NYHA/WHO functional class (NNT=3 and NNT=7.7 to 14.3 respectively),
dyspnoea score (ES [95%CI]: 1.6 [1.2; 1.9] and 4.5 [3.8; 5.1] for bosentan dosages of 250
mg/day and 500 mg/day, respectively) and hemodynamic measures – Table 4 in online
Supplementary material [36-37, 42]
A sub-analysis of 66 patients with connective tissue disease (CTD)-related PAH (CTD-PAH)
included in the above two RCTs, (79% were SSC patients), revealed a placebo-adjusted
improvement in 6MWT of 22 m in favour of bosentan (ES [95% CI]: 0.3 [-0.2; 0.8]) [43].
Analysis of the two pivotal RCTs and their long-term extension studies suggested that
bosentan may improve survival in SSC-PAH in comparison with historic controls (1-, 2- and
3-year survival: 82%, 67% and 64%, respectively, vs. 45%, 35% and 28%) [44]. Similarly,
Williams et al. demonstrated that SSC-PAH patients receiving bosentan (in addition to
standard therapy consisting of diuretics, digoxin, oxygen, warfarin, and, if clinically
indicated, prostanoids) had a significantly better survival (81% at one year, 71% at two years)
than a historic comparator group of SSC-PAH patients treated with standard therapy including
prostanoids (survival: 68% and 47% at one and two years, respectively (p=0.016)) [45].
On the basis of the results of RCTs, bosentan was recommended in the current guidelines of
the American College of Chest Physicians (ACCP) for the treatment of severe PAH (WHO
class III/IV) [46].

5. Two high quality RCTs indicate that sitaxentan improves exercise capacity, functional
class and some hemodynamic measures in PAH. At present, sitaxentan may also be
considered to treat SSc-PAH.

Two high quality (Jadad score 4) RCTs (STRIDE-1 and STRIDE-2) including 423 patients
with different forms of PAH, among which 63, (15%) had SSc-related PAH indicate that,
sitaxentan (a selective ETA endotelin receptor antagonist), administered orally at a dose of
100 mg/day and 300 mg/day for 12 to 18 weeks, significantly improved exercise capacity and
hemodynamics [39,47] – see Table 4 in online Supplementary material. Accordingly,
sitaxentan (100mg/day and 300mg/day) improved NYHA functional class compared with
placebo (NNT=7 for both doses assessed over 12 weeks) [39]. The improvement was even
greater in a STRIDE-1 subgroup of PAH patients being in WHO class III or IV, suggesting
that patients with more severe PAH may achieve greatest benefit from sitaxentan therapy –
Table 4 [48]. In view of the comparable efficacy of the two sitaxentan regimens and the fact
that the higher dose was associated with greater toxicity (discussed below), sitaxentan at a
dose of 100 mg/day is suggested in the treatment of PAH.
No studies or specific subgroup analyses investigating the efficacy of sitaxentan in SSc-PAH
have been published. A subanalysis of both pivotal trials combined the 110 patients with
CTD-PAH, of whom 63 (57%) had SSc-PAH, showed that 100mg/day revealed similar
improvement in 6MWT as in the overall STRIDE-1 study population (ES [95%CI] for
sitaxentan vs placebo: 0.3 [-0.2; 0.8]). One-year survival in 42 CTD-PAH patients receiving
Sitaxentan in open label studies was significantly better than in 25 CTD-PAH patients treated
with bosentan (98% vs 79%; p=0.0125), though the effects on 6MWT and functional class
were not different comparing the two drugs [50].
In view of its comparable efficacy and its similar toxicity profile, experts considered
sitaxentan as an alternative for bosentan in patients with SSc-related PAH. Open label
extension of STRIDE-2 suggested that sitaxentan (100 mg/day) may be safer than bosentan
(250mg/day) with regard to the frequency of liver test abnormalities (3% of the sitaxentan
group vs 18% of the bosentan group (p<0.03)) and premature discontinuation, either related to
hepatotoxicity (0% vs 14% for sitaxentan vs bosentan) or overall (20% vs 57% for sitaxentan
vs bosentan \( p=0.0005 \) [50]. Moreover, sitaxentan 100mg/day improved the clinical status in more than one-third of PAH patients in whom bosentan was ineffective [52]. Sitaxentan, as other ERAs, is potentially teratogenic and may reduce the efficacy of hormonal contraceptive therapy.

6. One high quality RCT indicates that sildenafil improves exercise capacity, functional class and some hemodynamic measures in PAH. Sildenafil may be considered to treat SSc-PAH.

One high quality RCT (Jadad score: 5) has demonstrated that sildenafil (a selective type 5 phosphodiesterase inhibitor), given orally at a dose of 20mg, 40mg or 80mg three times daily, significantly improved 6MWT results functional class, and hemodynamics over a 12-week period in PAH of different origin [53] – see Table 5 in online Supplementary material. Another RCT (Jadad score: 5), involving 26 PAH patients (of whom 2 with SSc-PAH) indicated that sildenafil (50mg twice daily for 4 weeks followed by 50mg three times per day) was comparable to - or even better than - bosentan in improving 6MWT, Borg dyspnea score, and cardiac index. [41] The improvement in exercise capacity was maintained to at least 1 year [53].

In a subgroup of 84 patients with CTD-PAH (including 38 SSc-PAH patients) sildenafil significantly improved walking distance \( p<0.05 \) for 60mg/day and 120mg/day), functional class (NNT from 4.0 to 2.9, depending on the sildenafil dose), mean PAP and PVR \( p<0.05 \) for 60 mg/d for both) in comparison to placebo. [54]. Sildenafil has been approved by the FDA for the treatment of PAH patients in WHO functional class II, III and IV [46]. The experts indicated that - as compared to bosentan - the amount of data confirming the efficacy and safety of sildenafil in SSc-PAH was sparse. Therefore, at present, sildenafil should be considered for the treatment of SSc-PAH patients in whom bosentan has been ineffective, or can not be used for safety reasons.

7. One high quality RCT indicates that continuous intravenous epoprostenol improves exercise capacity, functional class and hemodynamic measures in SSc-PAH. Sudden drug withdrawal may be life threatening. Intravenous epoprostenol should be considered for the treatment of patients with severe SSc-PAH.

One RCT (Jadad score: 3), involving 111 SSc-PAH patients, showed that epoprostenol, (continuous intravenous infusion, starting dose 2ng/kg/min i.v., 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 hemodynamic measures in SSc-PAH, as compared to conventional therapy [29]. The median 6MWT distance improved by 108m (95%CI: 55 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 dyspnea index and the dyspnea fatigue score improved significantly too. Beneficial hemodynamic 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. Based on the results of RCTs and two large long term observational studies, which have documented an improvement in survival of patients with iPAH treated with epoprostenol [56,57], intravenous epoprostenol has been approved by FDA for treatment of severe (WHO class III or IV) PAH.
Due to a very short half life, epoprostenol is administered through a permanent indwelling central venous catheter, that may favor adverse events: infections, pneumothorax, and haemorrhage [29]. Sudden disruption/withdrawal of i.v. epoprostenol (due to catheter/vein thrombosis and/or patient’s decision) may lead to life-threatening PAH rebound. Epoprostenol is contraindicated in severe left ventricular dysfunction and if symptoms of pulmonary edema develop during epoprostenol dose initiation which may be associated with pulmonary veno-occlusive disease [58]. Based on overall risk-to-benefit considerations, and in agreement with the current ACCP guidelines, experts recommend intravenous epoprostenol as treatment of choice in severe, therapy resistant SSc-PAH. [46] Although not included in the text of the present recommendations, other prostacyclin analogues are available and approved for treatment of PAH – see online Supplementary material. [59-61]

### III. SSc-related skin involvement

8. Two RCTs have shown that methotrexate improves skin score in early dSSc. Positive effects on other organ manifestations have not been established. Methotrexate may be considered for treatment of skin manifestations of early dSSc.

In one RCT (Jadad score 3), involving 29 SSc patients with dSSc or lSSc (mean duration of skin involvement: 3.2 years), methotrexate (intramuscular at a dose of 15mg/week for 24 weeks) showed a trend towards improvement of the Total Skin Score (TSS) (p=0.06 vs placebo) [62].

In the second RCT (Jadad score 5), involving 73 patients with early dSSc, methotrexate, given orally at a dose of 10mg per week for 12 months, decreased the University of California Los Angeles (UCLA) skin score (ES [95%CI] 0.5 [0.0; 1.0]) and the modified Rodnan skin score (mRSS) (ES [95%CI] 0.5 [0.0; 0.9]) as compared with placebo in an intention-to-treat analysis. Eleven out of 36 patients (31%) in the placebo group and 12 out of 35 patients (34%) in the methotrexate group dropped out prior to study completion, mainly due to treatment inefficacy. There were few premature discontinuations due to adverse events (NNH=16 and 34.5 in both RCTs, respectively) [62-63]. There were no significant differences in the mortality rate (3 versus 7; p<0.18), though the trend was in favor of methotrexate. [63]. Safety concerns associated with methotrexate include liver toxicity, pancytopenia, its potential teratogeneity and, possibly, the induction of lung injury/interstitial lung disease [62,64].

It should be recognized that cyclophosphamide has also been shown, in RCT, to improve skin changes in SSc patients and other agents such as mycophenolate mofetil, azathioprine or cyclosporine A are used to treat skin involvement, although their efficacy have not been studied so extensively.[65] – see also Table 3

### IV. Scleroderma interstitial lung disease

9. In view of the results from two high quality RCTs and despite its known toxicity, cyclophosphamide should be considered for treatment of SSc-related interstitial lung disease (SSc-ILD).

The efficacy and safety of cyclophosphamide in the treatment of SSc-ILD was evaluated in two high quality (Jadad score: 5) RCTs [65-66]. The first trial, involving 158 SSc patients with active alveolitis, demonstrated that cyclophosphamide given orally at a dose of 1-2 mg/kg/d improved lung function tests, dyspnoea score and quality of life over 12 months
compared with placebo. The placebo-corrected mean [95% CI] improvement in the forced vital capacity (FVC) and the total lung capacity (TLC) was 2.5% [0.3; 4.8%] and 4.1% [0.5; 7.7%] respectively (p<0.03 for both measures). Cyclophosphamide did not increase the lung diffusing capacity for carbon monoxide (DLCO). Cyclophosphamide improved the transitional dyspnea index (mean (SE): 1.4 (0.2)) whilst this index deteriorated in the placebo group (1.5 (0.4), p<0.001 for between group difference). Cyclophosphamide also improved the HAQ disability index, and the vitality- and health-transition domains of the SF36 (p<0.05 vs placebo for both measures) [65].

The second trial evaluated cyclophosphamide (intravenously at a dose of 600 mg/m² per month) versus placebo in 45 SSc patients with SSc-ILD. Active treatment included 6 infusions of cyclophosphamide given at 4-week intervals followed by oral azathioprine (2.5 mg/kg/day) or placebo for 6 months. Prednisolone (20mg 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 cyclophosphamide, which just missed statistical significance (p=0.08). DLco and other outcome measures did not improve [66]. There was unanimous consensus about cyclophosphamide dose and duration of treatment to be tailored individually dependent on the clinical condition and response. Potential risks of bone marrow suppression, teratogeneity, gonadal failure and hemorrhagic cystitis must be always considered [67].

V. Scleroderma renal crisis (SRC)

10. Despite the lack of RCTs, experts believe that angiotensin converting enzyme inhibitors (ACEi) should be used in the treatment of scleroderma renal crisis.

RCTs evaluating the efficacy of ACEi in the treatment of SRC are lacking. Since the first report demonstrating a beneficial effect of ACEi in 2 patients with SRC [68], numerous case reports and uncontrolled studies have reported about ACEi in SRC. Prospective analysis of 108 patients with SRC has suggested that patients on ACEi (captopril in 47 and enalapril in 8) had a significantly better survival rate at one year (76%) and 5 years (66%) compared to patients not on ACEi (15% at one and 10% at 5 years, respectively) Treatment with ACEi was significantly associated with better survival in SRC, after adjustment for age and blood pressure (p<0.001). [69] Another prospective uncontrolled study of 145 patients with SRC treated with ACEi demonstrated survival rates at 5 and 8 years after the onset of SRC of 90% and 85% respectively [70]. Additionally, treatment with ACEi decreased the need of permanent dialysis [69,70]. Published evidence includes mainly captopril and enalapril.

It is highly unlikely that formal RCTs will be conducted in this rare condition with high mortality.

11. Four retrospective studies suggest that steroids are associated with a higher risk of SRC. Patients on steroids should be carefully monitored for blood pressure and renal function.

The impact of steroid use on the development of SRC was evaluated in four retrospective studies involving 544 SSc patients, all suggesting an association between steroid treatment and the occurrence of SRC [71-74]. A case-control analysis showed that 36% of patients with SRC had received prednisone≥15mg/day or equivalent within 6 months preceding the onset of SRC, as compared with 12% matched controls (OR [95%CI]: 4.4 [2.1-9.4], p<0.0001) [72]. In another study, recent exposure to corticosteroids was noted in 61% of SRC patients, and the exposure to corticosteroids during the previous 3 months was associated with a higher risk of SRC (RR [95%CI]: 6.2 [2.2-17.6]).[74] An analysis of the main risk factors for SRC
suggested that the patients with a high skin score, joint contractures and prednisone use (≤ 10 mg/d in 9 out 10 patients) were at higher risk (43% versus 21% of patient without steroids) for SRC [73].

VI. SSc-related gastrointestinal disease

12. Despite the lack of specific RCTs, experts believe that proton pump inhibitors (PPIs) should be used for prevention of SSc-related gastroesophageal reflux disease, esophageal ulcers and strictures.
Specific RCTs for the efficacy of PPIs in patients with SSc are lacking. The efficacy of PPIs in the treatment of gastroesophageal reflux disease (GERD) in a general population is well documented in meta-analyses of RCTs [75-76].

13. Despite the lack of specific RCTs, experts believe that prokinetic drugs should be used for the management of SSc-related symptomatic motility disturbances (dysphagia, GERD, early respond in the satiety, bloating, pseudoobstruction, etc.)
Small RCTs involving SSc or CTD patients indicate that short-term usage of cisapride has a beneficial effect on gastric emptying and lower esophageal sphincter pressures [77-81]. However, in many countries cisapride has been either withdrawn or has had limited use due to reports about long QT syndrome due to cisapride, which predisposes to severe arrhythmias. Long-term efficacy RCTs of other prokinetics in SSc were not found. Several non-randomised or uncontrolled studies suggest that prokinetics may improve gastrointestinal signs and symptoms in SSc patients [82-84].
Several prokinetic drugs have shown beneficial in RCTs involving patients with other than SSc-related dismotility disorders or are under evaluation (for review see ref 85-86). Whether these drugs would be effective in the treatment of SSc-related symptomatic motility disturbances is at present only speculative and needs to be investigated.

14. Despite the lack of specific RCTs, experts believe that, when malabsorption is due to bacterial overgrowth, rotating antibiotics may be useful in SSc.

No RCT regarding the efficacy of antibiotics in the treatment of SSc-related bacterial overgrowth or malabsorption were found. In general, current treatment of small intestinal bacterial overgrowth is based on empirical courses of broad-spectrum antibiotics such as quinolones or amoxicillin-clavulanic acid. The principles of diagnosis and treatment strategies of this condition have been summarized in recent excellent review. [87]

Discussion
The present set of recommendations addresses only a limited number of the most relevant pharmacological treatments of SSc. Many were tested in RCTs, although some, even in the absence of RCTs, were felt by the expert committee to be indicated for SSc. Since SSc has a heterogeneous clinical course and is an uncommon disease, many treatment options have not yet been able to be appropriately tested. It should be recognized that “absence of evidence for efficacy” does not imply that “efficacy is absent”. Indeed, some treatment options which were not translated into recommendations because of lack of evidence, were considered important or promising by the expert committee and were included in the research agenda – Table 2 and 3.
Due to the scarcity of high-quality RCTs solely involving SSc patients, several recommendations are based on evidence extrapolated from other diseases (such as iPAH, or GERD). These diseases may differ from SSc-related complications in clinical course and prognosis.

There are also other treatment options for the management of SSc patients, such as physiotherapy, education, new experimental therapies, etc. which were beyond the scope of this project or could not be included because of the lack of expert consensus.

Medications that are disease modifying for SSc in terms of mortality are lacking, and the efficacy of the treatments recommended here is often only modest to moderate. Nevertheless, given no other options these less than optimal treatments are still worthwhile. This set of recommendations should be helpful to make clinical decisions but should always be used in the context of the patient, clinical judgment and with the balance of efficacy and toxicity in mind.

In view of the heterogeneity of SSc, the complexity of the diagnostic evaluation and the wide array of available treatment options, experts believe that referral of patients with SSc to a specialized center should be strongly considered.

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References


17


<table>
<thead>
<tr>
<th>No</th>
<th>Recommendation</th>
<th>Strength of recommendation</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>I. SSc-related digital vasculopathy (Raynaud’s phenomenon, digital ulcers)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>A meta-analysis on dihydropiridine-type calcium channel blockers and one meta-analysis on prostanoids indicate that nifedipine and i.v. iloprost reduce the frequency and severity of SSc-related Raynaud’s phenomenon attacks. Dihydropiridine-type calcium channel blockers, usually oral nifedipine, should be considered for first-line therapy for SSc-related Raynaud’s phenomenon, and intravenous iloprost, or other available i.v. prostanoids, for severe SSc-related Raynaud’s phenomenon.</td>
<td>A</td>
<td>14, 24</td>
</tr>
<tr>
<td>2.</td>
<td>Two RCTs indicate that intravenous prostanoids (particularly i.v. iloprost) are efficacious in healing digital ulcers in patients with SSc. Intravenous prostanoids (in particular iloprost) should be considered in the treatment of active digital ulcers in patients with SSc.</td>
<td>A</td>
<td>21, 22</td>
</tr>
<tr>
<td>3.</td>
<td>Bosentan has no proven efficacy in the treatment of active digital ulcers in SSc patients. Bosentan has proven efficacy in two high quality RCTs to prevent digital ulcers in diffuse SSc patients, in particular in those with multiple digital ulcers. Bosentan should be considered in diffuse SSc with multiple digital ulcers after failure of calcium channel blockers and, usually, prostanoid therapy.</td>
<td>A</td>
<td>30, 31, 32</td>
</tr>
<tr>
<td>II</td>
<td>II. SSc-related pulmonary arterial hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Two high quality RCTs indicate that bosentan improves exercise capacity, functional class and some hemodynamic measures in pulmonary arterial hypertension. Bosentan should be strongly considered to treat SSc-related pulmonary arterial hypertension.</td>
<td>A/B</td>
<td>36, 37</td>
</tr>
<tr>
<td>5.</td>
<td>Two high quality RCTs indicate that sitaxentan improves exercise capacity, functional class and some hemodynamic measures in pulmonary arterial hypertension. At present, sitaxentan may also be considered to treat SSc-related pulmonary arterial hypertension.</td>
<td>A/B</td>
<td>39, 47, 48</td>
</tr>
<tr>
<td>6.</td>
<td>One high quality RCT indicates that sildenafil improves exercise capacity, functional class and some hemodynamic measures in pulmonary arterial hypertension. Sildenafil may be considered to treat SSc-related pulmonary arterial hypertension.</td>
<td>A/B</td>
<td>53</td>
</tr>
<tr>
<td>7.</td>
<td>One high quality RCT indicates that continuous intravenous epoprostenol improves exercise capacity, functional class</td>
<td>A</td>
<td>29</td>
</tr>
</tbody>
</table>
and hemodynamic measures in SSc-related pulmonary arterial hypertension. Sudden drug withdrawal may be life threatening. Intravenous epoprostenol should be considered for the treatment of patients with severe SSc-related pulmonary arterial hypertension.

### III SSc-related skin involvement

8. Two RCTs 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 | 62, 63 |

### IV Scleroderma interstitial lung disease

9. In view of the results from two high quality RCTs and despite its known toxicity, cyclophosphamide should be considered for treatment of SSc-related interstitial lung disease.

| A | 65, 66 |

### V Scleroderma renal crisis

10. Despite the lack of RCTs, experts believe that angiotensin converting enzyme (ACE) inhibitors should be used in the treatment of scleroderma renal crisis.

| C | 68, 69, 70 |

11. Four retrospective studies suggest that steroids are associated with a higher risk of scleroderma renal crisis. Patients on steroids should be carefully monitored for blood pressure and renal function.

| C | 71, 72, 73, 74 |

### VI SSc-related gastrointestinal disease

12. Despite the lack of specific RCTs, experts believe that proton pump inhibitors should be used for prevention of SSc-related gastroesophageal reflux, esophageal ulcers and strictures.

| B | 75, 76 |

13. Despite the lack of specific RCTs, experts believe that prokinetic drugs should be used for the management of SS-related symptomatic motility disturbances (dysphagia, GERD, early satiety, bloating, pseudoobstruction, etc.)

| C | 77 - 84 |

14. Despite the lack of specific RCTs, experts believe that, when malabsorption is due to bacterial overgrowth, rotating antibiotics may be useful in SSc patients.

| D |  |
Table 2. Research agenda

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Evaluation of the efficacy and safety of cyclophosphamide in the treatment of early diffuse SSc</td>
</tr>
<tr>
<td>2.</td>
<td>Evaluation of efficacy and safety of mycophenolate mofetil and azathioprine in the treatment of SSc</td>
</tr>
<tr>
<td>3.</td>
<td>Evaluation of the efficacy and safety of sildenafil in the treatment of SSc-related Raynaud’s phenomenon and digital ulcers</td>
</tr>
<tr>
<td>4.</td>
<td>Evaluation of the efficacy and safety, angiotensin converting enzyme (ACE) inhibitors in prevention of scleroderma renal crisis</td>
</tr>
<tr>
<td>5.</td>
<td>Evaluation of calcium channel blockers in prevention of SSc-related pulmonary arterial hypertension (PAH)</td>
</tr>
</tbody>
</table>
Table 3. Comments of the expert committee concerning research questions that did not yield a formal recommendation because of lack of appropriate evidence.

<table>
<thead>
<tr>
<th>Research question</th>
<th>Comment from the expert committee</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACE INHIBITORS AND SARTANS</strong></td>
<td></td>
</tr>
<tr>
<td>1. Do angiotensin receptor antagonists (sartans) have beneficial effects in systemic sclerosis?</td>
<td>One RCT indicates that losartan may reduce the frequency and severity of RP attacks. Losartan may be recommended for the treatment of RP secondary to SSc.</td>
</tr>
<tr>
<td><strong>STEROIDS</strong></td>
<td></td>
</tr>
<tr>
<td>1. Are steroids beneficial in systemic sclerosis?</td>
<td>The expert opinion is that low dose of steroids are commonly used for treatment of inflammatory arthritis in patients with SSc but its efficacy is not substantiated by RCTs.</td>
</tr>
<tr>
<td><strong>HEMATOPOIETIC STEM CELL TRANSPLANTATION</strong></td>
<td></td>
</tr>
<tr>
<td>1. Does hematopoietic stem cell transplantation have beneficial effects in systemic sclerosis?</td>
<td>The cumulative phase I-II experience supports the use of HSCT in a selected poor-prognosis subgroup of SSc. Currently, transplantation should be performed only in the context of a RCT.</td>
</tr>
<tr>
<td><strong>IMMUNOSUPPRESSIVES</strong></td>
<td></td>
</tr>
<tr>
<td>1. Is there any evidence of beneficial effects of cyclosporin A in SSc?</td>
<td>Two RCTs with cyclophosphamide have reported efficacy on skin, quality of life and function. Uncontrolled and retrospectively controlled studies with some immunosuppressive regimens (such as azathioprine, mycophenolate mofetil, cyclosporine A) have reported efficacy in selected manifestations of systemic sclerosis. Their efficacy has to be further evaluated in randomized controlled trials. (Research agenda) Of note, experts believe that great caution is necessary when using cyclosporine because it may decrease renal function and induce hypertension.</td>
</tr>
<tr>
<td>2. Is there any evidence of beneficial effects of mycophenolate mofetil in SSc?</td>
<td></td>
</tr>
<tr>
<td>3. Is there any evidence of beneficial effects of azathioprine in SSc?</td>
<td></td>
</tr>
<tr>
<td><strong>OTHER TREATMENTS</strong></td>
<td></td>
</tr>
<tr>
<td>1. Which drugs are beneficial in subcutaneous calcinosis in SSc?</td>
<td>Drugs that improve calcinosis are currently lacking.</td>
</tr>
<tr>
<td>2. Is there any evidence that NSAIDs are harmful in SSc?</td>
<td>Experts believe that NSAIDs are in general not more harmful in SSc than in the general population. But formal evidence is lacking. NSAID toxicity in the general population is well recognised.</td>
</tr>
</tbody>
</table>
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Haifa, Israel (A Balbir Gurmann)
Re: I. SSc-related digital vasculopathy (Raynaud’s phenomenon, digital ulcers)

It should be recognized that, in addition to CCBc and prostanoids, there are many other therapies which are in use for treatment of SSc-related Raynaud’s phenomenon such as nitrate preparations, anti-platelet agents, angiotensin receptor blockers, or anti-oxidants. Although these therapies have not been studied so extensively they appear beneficial for some at least cases. One RCT, included in the above meta-analysis, showed losartan (an antagonist of angiotensin II receptor type 1) given at a dose of 50 mg/day to be superior than nifedipine 40 mg/day in reducing the frequency (ES [95%CI]: 0.8 [-1.5; 0.1] for losartan vs nifedipine) and severity (ES [95%CI]: 0.5 [-1.2; 0.3]) of SSc-related RP over 12 week period. [13]

Re: II. SSc-related pulmonary arterial hypertension

Endothelin receptor antagonists (ERAs)

ERAs, tested for a period of 12 to 16 weeks against placebo, significantly improved exercise capacity (mean difference [95% CI] in 6 minute walk test (6MWT): 37m, [22 to 52m]), Borg dyspnea score (ES [95% CI]: 0.8 [0.0; 1.7]), pulmonary artery pressure (PAP) (WMD [95% CI]: 4.4, [1.9; 6.8]) and cardiac index (CI) (WMD [95% CI]: 0.5 [0.2; 0.8]).

Although not included in the text of the present recommendations, other then epoprostenol prostacyclin analogues are available and approved for treatment of PAH. These include subcutaneous treprostenil, and inhaled iloprost [59-60]. Treprostenil has shown to improve the 6MWT (p<0.006 vs placebo), the dyspnea score and hemodynamic parameters in a heterogenous population of PAH patients. In a sub-group of CTD-PAH (of whom 50% had SSc-related PAH) treprostinil has shown to significantly improve the CI (ES [95%CI] 0.4 [0.0; 0.9]), and the fatigue-dyspnea score (ES [95%CI] 0.5 [0.0; 0.9]), and there was a trend towards improvement in 6MWT (ES [95%CI] 0.2 [-0.2; 0.7]).[61] Efficacy of treprostenil was dose related, and subcutaneous administration may be limited by infusion site reaction and pain [58]. No studies or specific subgroup analyses on efficacy of inhaled iloprost in SSc-PAH only were found.

Prostacyclines

Although not included in the text of the present recommendations, other prostacyclin analogues are available and approved for treatment of PAH [59-61]. These include subcutaneous treprostenil, and inhaled iloprost [59-60]. Treprostenil has shown to improve the 6MWT (p<0.006 vs placebo), the dyspnea score and hemodynamic parameters in a heterogenous population of PAH patients. In a sub-group of CTD-PAH (of whom 50% had SSc-related PAH) treprostinil has shown to significantly improve the CI (ES [95%CI] 0.4 [0.0; 0.9]), and the fatigue-dyspnea score (ES [95%CI] 0.5 [0.0; 0.9]), and there was a trend towards improvement in 6MWT (ES [95%CI] 0.2 [-0.2; 0.7]).[61] Efficacy of treprostenil was dose related, and subcutaneous administration may be limited by infusion site reaction and pain [59]. No studies or specific subgroup analyses on efficacy of inhaled iloprost in SSc-PAH only were found.
<table>
<thead>
<tr>
<th>dose (Study duration)</th>
<th>6MWT</th>
<th>mPAP</th>
<th>PVR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>125/d for 4 weeks then 250mg/d or 500 mg/d</td>
<td>+76.0 [0.1 to 1.6]</td>
<td>0.9 [0.1 to 1.6]</td>
<td>0.5 [-1.3 to 0.2]</td>
<td>-415 [-1.3 to 0.2]</td>
</tr>
<tr>
<td>12 weeks (ref. 37)</td>
<td>+44 p&lt;0.001</td>
<td>0.7 [0.4 to 1.0]</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Sitaxentan</td>
<td>50mg/d</td>
<td>+24.2 [-0.1 to 0.7]</td>
<td>0.2 [-0.1 to 0.7]</td>
<td>NA</td>
</tr>
<tr>
<td>100 mg/d</td>
<td>+35 P=0.01</td>
<td>0.3 [-0.1 to 0.7]</td>
<td>-4.0 ns</td>
<td>-269 P&lt;0.001</td>
</tr>
<tr>
<td>12 weeks (ref. 40)</td>
<td>+65 p=0.0002</td>
<td>0.7 [0.2 to 1.2]</td>
<td>-5.1</td>
<td>-359</td>
</tr>
<tr>
<td>18 weeks* (ref. 49)</td>
<td>+31.4 P=0.03</td>
<td>0.4 [0.0 to 0.8]</td>
<td>-6.0</td>
<td>-242 P&lt;0.001</td>
</tr>
<tr>
<td>Sitaxentan</td>
<td>300 mg/d</td>
<td>+33 P=0.01</td>
<td>0.3 [-0.1 to 0.7]</td>
<td>-6.0</td>
</tr>
<tr>
<td>12 weeks (ref. 40)</td>
<td>+33 P=0.01</td>
<td>0.3 [-0.1 to 0.7]</td>
<td>-6.0</td>
<td>-242 P&lt;0.001</td>
</tr>
</tbody>
</table>

*subgroup analysis of PAH patients in WHO class III/IV only; the results for combined doses of 100mg/d and 300mg/d (Langleben JCP2004).
Table 5. Efficacy of different dose regimens of sildenafil on physical capacity, functional status and hemodynamic measures (SUPER study) (53)

<table>
<thead>
<tr>
<th>Sildenafil dose</th>
<th>6MWT</th>
<th>WHO class</th>
<th>mPAP</th>
<th>PVR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TE (m)</td>
<td>ES [95%CI]</td>
<td>TE (mmHg)</td>
<td>ES [95%CI]</td>
<td>TE (dyn.s.cm⁻¹)</td>
</tr>
<tr>
<td>20mg x 3/d 12 weeks</td>
<td>38</td>
<td>0.5</td>
<td>4.6</td>
<td>-1.5</td>
<td>-0.2</td>
</tr>
<tr>
<td></td>
<td>P&lt;0.001</td>
<td>(0.1 to 0.8)</td>
<td></td>
<td>P=0.04</td>
<td></td>
</tr>
<tr>
<td>40 mg x 3/d 12 weeks</td>
<td>45</td>
<td>0.6</td>
<td>3.5</td>
<td>-2.0</td>
<td>-0.2</td>
</tr>
<tr>
<td></td>
<td>P&lt;0.001</td>
<td>(0.2 to 0.9)</td>
<td></td>
<td>p=0.01</td>
<td></td>
</tr>
<tr>
<td>80 mg x 3/d 12 weeks</td>
<td>42</td>
<td>0.5</td>
<td>2.9</td>
<td>-4.1</td>
<td>-0.33</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.001</td>
<td>(0.2 to 0.8)</td>
<td></td>
<td>P&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

CI=cardiac index; TE=placebo-corrected treatment effect; ES=effect size; mPAP=mean pulmonary artery pressure; NNT=number needed to treat; PVR=pulmonary vascular resistance
EULAR recommendations for the treatment of systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group (EUSTAR)


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