Supplement

Update of EULAR recommendations for the treatment of systemic sclerosis

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SUPPLEMENTARY METHODS

Selection process of clinical questions: web-based Delphi exercise

Each participant had received an e-mail invitation allowing personalised access to a web-based questionnaire (SurveyMonkey ®). Reminders were sent to non-responders after 1 and 2 weeks. Participants rated the appropriateness of each clinical question for systemic sclerosis (SSc) treatment recommendations on a scale of 1 (not appropriate at all) to 9 (very appropriate). Clinical questions were accepted if over 50% of participants scored 7-9, with less than 30% scoring 1-3 (no disagreement). Questions with over 50% of scores between 1-3 were rejected if less than 30% scored 7-9 (no disagreement). Questions with a median appropriateness score 4-6 and questions with higher or lower medians having disagreement were rated ‘ambiguous’ and subjected to a next Delphi round. Participants also could submit new clinical questions. The remaining ‘ambiguous’ questions and new clinical questions were submitted to the participants, with provision of previous scores, in two next rounds. Participants were only included in rounds 2 and 3 if they had responded in round 1.

Table S1. List of research questions accepted for systematic literature research during the first recommendation meeting: Paris June 10-11th, 2014

I. ***Corticosteroids***
1. Do corticosteroids have beneficial effects on interstitial lung disease in SSc? 2. Do corticosteroids contribute to the development of scleroderma renal crisis?
II. ***Cyclophosphamide***
1. Is cyclophosphamide beneficial in interstitial lung disease in SSc? 2. Does cyclophosphamide have beneficial effects on skin fibrosis in SSc?
III. ***Mycophenolate mofetil***
1. Does mycophenolate mofetil have beneficial effects on interstitial lung disease in SSc? 2. Does mycophenolate mofetil have beneficial effects on skin fibrosis in SSc?
IV. ***Methotrexate***
1. Does methotrexate have beneficial effects on skin fibrosis in SSc? 2. Does methotrexate have beneficial effects on musculoskeletal involvement (arthritis, myositis, tendinitis, contractures) in SSc? 3. Which are effects of methotrexate on interstitial lung disease in SSc?
V. ***Other immunosuppressive drugs***
1. Does azathioprine have beneficial effects on interstitial lung disease in SSc?
VI***. Hematopoietic stem cells transplantation***
1. Does hematopoietic stem cell transplantation have beneficial effects on survival, event-free survival, skin fibrosis, interstitial lung disease, and patient reported outcomes in SSc?
VII***. Anti-CD20 therapy (Rituximab)***
1. Do anti-CD20 therapies (rituximab) have beneficial effects on skin fibrosis in SSc? 2. Do anti-CD20 therapies (rituximab) have beneficial effects on interstitial lung disease in SSc?
VIII***. TNF antagonists***
1. Do TNF antagonists have beneficial effects on arthritis in SSc?
IX***. Tocilizumab***
1. Does tocilizumab have beneficial effects on skin fibrosis in SSc? 2. Does tocilizumab have beneficial effects on interstitial lung disease in SSc? 3. Does tocilizumab have beneficial effects on musculoskeletal involvement (arthritis, myositis, tendinitis, contractures) in SSc?
X***. Calcium channel blockers***
1. Do calcium channel blockers have beneficial effects on Raynaud's phenomenon in SSc? 2. Do calcium channel blockers have beneficial effects on digital ulcers in SSc?
XI***. ACE-inhibitors***

1. Do ACE-inhibitors prevent scleroderma renal crisis? 2. Do ACE-inhibitors improve scleroderma renal crisis?
XII***. Angiotensin receptor antagonist (Sartans)***
1. Do sartans prevent scleroderma renal crisis? 2. Do sartans improve scleroderma renal crisis?
XIII***. Statins***
1. Do statins prevent digital ulcers in SSc? 2. Do statins heal digital ulcers in SSc?
XIV***. Prostacyclins***
1. Do prostacyclin analogues have beneficial effects on Raynaud's phenomenon in SSc? 2. Do prostacyclin analogues have beneficial effects on digital ulcers in SSc? 3. Do prostacyclin analogues have beneficial effects on pulmonary arterial hypertension in SSc? 4. Do prostacyclin analogues improve scleroderma renal crisis in SSc?
XV***. Endothelin receptor antagonists***
1. Do endothelin receptor antagonists have beneficial effects on Raynaud's phenomenon in SSc? 2. Do endothelin receptor antagonists have beneficial effects on digital ulcers in SSc? 3. Do endothelin receptor antagonists have beneficial effects on pulmonary arterial hypertension in SSc?
XVI***. Selective PDE-5 inhibitors***
1. Do selective PDE-5 inhibitors have beneficial effects on Raynaud's phenomenon in SSc? 2. Do selective PDE-5 inhibitors have beneficial effects on digital ulcers in SSc? 3. Do selective PDE-5 inhibitors have beneficial effects on pulmonary arterial hypertension in SSc? 4. Do selective PDE-5 inhibitors have beneficial effects on erectile dysfunction in SSc?
XVII***. Anti-platelet aggregant/ anti-coagulant***
1. Do anti-platelet drugs have beneficial effects on digital ulcers in SSc?
XVIII**. Proton Pump Inhibitors**
1. Do proton pump inhibitors have beneficial effects on esophageal involvement in SSc?
XIX**. Prokinetic agents**
1. Do prokinetic drugs have beneficial effects on gastrointestinal involvement in SSc?
XX**. Non steroidal anti-inflammatory drugs (NSAIDs)**
1. Do NSAIDs increase the risk of scleroderma renal crisis in SSc?
XXI**. Antibiotics**
1. Do antibiotics have beneficial effects on small intestinal bacterial overgrowth in SSc?
XXII**. Other treatments**
1. Does hydroxychloroquine have beneficial effects on arthritis in SSc? 2. Does fluoxetine have beneficial effects on Raynaud's phenomenon in SSc? 3. Does riociguat have beneficial effects on pulmonary arterial hypertension in SSc?
XXIII**. General questions**

1. Does local wound care have beneficial effects on digital ulcers in SSc?
2. Does lymph drainage have beneficial effects on hand function in systemic sclerosis?

ACE=angiotensin converting enzyme, PDE=phosphodiesterase, SSc=systemic sclerosis.

Systematic literature search

Table S2. Combination of keywords, used for each question, to perform the systematic literature search.

Category	Combination of keywords
CALCIUM CHANNEL BLOCKERS	"(calcium channel blockers OR Nitrendipine OR Nisoldipine OR Nimodipine OR Nifedipine OR Nicardipine OR Isradipine OR Felodipine OR Amlodipine OR Dihydropyridines OR verapamil OR diltiazem) AND (systemic sclerosis OR scleroderma OR CREST)"
PROSTACYCLINS	"(prostanoids OR iloprost OR beraprost OR cisaprost OR treprostenil OR epoprostenol) AND (systemic sclerosis OR scleroderma OR CREST)"
ENDOTHELIN RECEPTOR ANTAGONISTS	"(endothelin receptor antagonists OR ambrisentan OR bosentan OR macitentan) AND (systemic sclerosis OR scleroderma OR CREST)"
SELECTIVE PDE-5 INHIBITORS	"(phosphodiesterase Inhibitors OR sildenafil OR tadalafil OR vardenafil) AND (systemic sclerosis OR scleroderma OR CREST)"
ACE-INHIBITORS	"(ACE inhibitors OR Angiotensin converting enzyme inhibitors) AND (systemic sclerosis OR scleroderma OR CREST)"
ANGIOTENSIN RECEPTOR ANTAGONISTS (SARTANS)	"(Angiotensin receptor antagonists OR losartan) AND (systemic sclerosis OR scleroderma OR CREST)"
CORTICOSTEROIDS	"(steroids OR prednisolone OR prednisone OR methylprednisolone OR dexamethasone OR glucocorticoids) AND (systemic sclerosis OR scleroderma OR CREST)"
NON STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)	"(NSAIDs OR Non-steroidal anti-inflammatory drugs OR cyclooxygenase inhibitors OR COX inhibitors) AND (systemic sclerosis OR scleroderma OR CREST)"
HEMATOPOIETIC STEM CELLS TRANSPLANTATION	"(autologous stem cell transplantation OR stem cell transplantation) AND (systemic sclerosis OR scleroderma OR CREST)"
CYCLOPHOSPHAMIDE	"(cyclophosphamide OR endoxan) AND (systemic sclerosis OR scleroderma OR CREST)"
MYCOPHENOLATE MOFETIL	"(mycophenolate mofetil OR mycophenolic acid OR CellCept AND (systemic sclerosis OR scleroderma OR CREST)"

METHOTREXATE	"methotrexate AND (systemic sclerosis OR scleroderma OR CREST)"
OTHER IMMUNOSUPPRESSIVE DRUGS	"(azathioprine OR imuran) AND (systemic sclerosis OR scleroderma OR CREST)"
ANTI-CD20 THERAPY (RITUXIMAB)	"(rituximab OR rituxan) AND (systemic sclerosis OR scleroderma OR CREST)"
TNFα ANTAGONISTS	"(TNFα inhibitors OR TNFα antagonists OR etanercept OR adalimumab OR infliximab, golimumab OR certolizumab) AND (systemic sclerosis OR scleroderma OR CREST)"
TOCILIZUMAB	"tocilizumab AND (systemic sclerosis OR scleroderma OR CREST)"
STATINS	"(statins OR HMG CoA Reductase Inhibitors) AND (systemic sclerosis OR scleroderma OR CREST)"
ANTI-PLATELET AGGREGANT/ ANTI-COAGULANT	"(anti-platelet OR anticoagulants OR aspirin, acetylsalicylic OR dipyridamole OR warfarin) AND (systemic sclerosis OR scleroderma OR CREST)"
PROTON PUMP INHIBITORS	"proton pump inhibitors AND (systemic sclerosis OR scleroderma OR CREST)"
PROKINETICS	"(prokinetic OR clebopride OR mosapride OR erythromycin OR octreotide OR misoprostol OR metoclopramide OR domperidone OR cisapride OR prucalopride) AND (systemic sclerosis OR scleroderma OR CREST)"
ANTIBIOTICS	"(antibiotics OR gastrointestinal OR malabsorption OR anorectal) AND systemic sclerosis OR scleroderma OR CREST)"
OTHER TREATMENTS	"fluoxetine AND (systemic sclerosis OR scleroderma OR CREST)" "(ulcer OR wound OR gangrene) AND (systemic sclerosis OR scleroderma OR CREST)" "riociguat AND (systemic sclerosis OR scleroderma OR CREST)"
GENERAL QUESTION	"lymph drainage AND (systemic sclerosis OR scleroderma OR CREST)"

ACE=angiotensin converting enzyme, COX= cyclooxygenase, CREST (syndrome)= calcinosis, Raynaud phenomenon, oesophageal dysmotility, sclerodactyly, and telangiectasia (syndrome), HGM CoA=Hydroxy-methyl-glutaryl-coenzyme A, PDE=phosphodiesterase, TNF=tumor necrosis factor.

Inclusion/exclusion criteria

A study could be included if its design was a meta-analysis of randomized controlled trials (RCTs), a systematic review, a RCT, a controlled trial, a case-control study, or

an uncontrolled trial/cohort study/case series. Cross sectional studies, case reports and case series with less than five patients with SSc were excluded.

Patients included in the study had to be adults with definite SSc, according to the ACR classification criteria, or as classified according to subtype as defined by LeRoy et al., or according to the ACR-EULAR classification criteria.[1-3] Studies concerning patients with other diagnoses, such as Raynaud phenomenon or pulmonary arterial hypertension (PAH), were only included if subgroup analysis of SSc patients was provided and the subgroups were larger than n=5.

Studies were only included if studying a treatment addressed in the clinical questions as selected, in any dose administered by any route.

Classifying and selecting evidence

For each clinical question, only the studies within the highest level of available evidence for each intervention were reviewed for critical appraisal and data extraction.[4-5] For intended effects, the most recent meta-analysis of RCTs (level Ia) was reviewed for each intervention if available, and any RCTs (level Ib) published since the meta-analysis was conducted were also considered. Else, studies within the next highest level of evidence were regarded. For unintended effects (toxicity), meta-analyses (level Ia), RCTs (level Ib) and non-randomized controlled studies (level 2) were always all considered.

Quality appraisal

The articles fulfilling the inclusion criteria underwent quality appraisal by AK or MB (supervised by JA) guided by JF, using a standard scoring sheet. For quality appraisal, a scale such as the Cochrane ‘Risk of Bias’ tool can be preferred.

However, as this was an update of the 2009 recommendations, we used the same criteria as used previously: the Jadad scale and an item for using intention-to-treat analysis.[6-8] The Jadad scale contains three questions: 1) Was the study described as randomized? 2) Was the study described as double blind? 3) Was there a description of withdrawals and dropouts? Each question has a yes (1) or no (0) response. For every clinical question, the quality appraisal of the single studies was summarized in a table, together with the extracted data.

Data extraction

Data were extracted using standard data extraction forms on the full reports, not blinded for authors and journal, by AK or MB, supervised by OKB and JA. Descriptive data included: first author, publication year, journal name and Impact Factor, participants' age and sex, definition of SSc, trial duration and design, type of treatment, type of comparator, information on dosage and route, number of patients in treatment and comparator groups, and the outcome measures used to assess efficacy. All reported outcomes were retrieved from all included studies. For continuous outcome data, such as the modified Rodnan skin score, mean (SD) of the within group changes were extracted and effect sizes were calculated whenever possible. For binary outcome data, such as response (yes/no), the proportions of patients with the outcome were calculated and the number-needed-to-treat (NNT) was calculated. If relevant, a number-needed-to-harm was calculated analogously, based on the number of discontinuations secondary to adverse events, the number of serious adverse events according to the FDA definition including the number of deaths.

SUPPLEMENTARY RESULTS

Number of studies identified by the systematic literature research

Literature search using combination of key words given in Table S2 identified altogether 8771 papers of which 3335 were papers found during search performed for the current update of the recommendations. Finally, after reading title, abstract or full text, 462 articles remained, were analyzed in detail and considered during second recommendation meeting, of which 181 were papers found during search performed for the current update of the recommendations.

Table S3. Comments of the expert committee concerning research questions that did not yield a formal recommendation because of lack of appropriate evidence

Research question	Comment from the expert committee
Corticosteroids 1.Do corticosteroids have beneficial effects on interstitial lung disease in SSc (SSc-ILD)?	There is no evidence from RCTs that glucocorticoids have beneficial effect on SSc-ILD.
Cyclophosphamide 1. Does cyclophosphamide have beneficial effects on skin fibrosis in SSc?	Evidence from one RCT (Scleroderma Lung Study) and from prospective observational studies indicate that cyclophosphamide has a beneficial effect on skin in patients with diffuse SSc. The efficacy of cyclophosphamide for skin in diffuse SSc needs more evidence.
Mycophenolate mofetil 1. Does mycophenolate mofetil have beneficial effects on interstitial lung disease in SSc? 2. Does mycophenolate mofetil have beneficial effects on skin fibrosis in SSc?	Evidence from retrospective and prospective observational studies and from case series indicate that mycophenolate mofetil has beneficial effect on skin and lung function in SSc. The efficacy of mycophenolate mofetil for skin and lung in SSc needs further evaluation in RCT. The results of a RCT comparing mycophenolate mofetil with cyclophosphamide in patients with SSc-ILD are awaited.
Methotrexate 1. Does methotrexate have beneficial effects on musculoskeletal involvement (arthritis, myositis, tendinitis, contractures) in SSc?	There is insufficient evidence to recommend methotrexate for musculoskeletal involvement in SSc patients. More evidence is needed.

2. Which are effects of methotrexate on interstitial lung disease in SSc?	There is insufficient evidence to either recommend or reject use of methotrexate in SSc-related interstitial lung disease
Other immunosuppressive drugs 1. Does azathioprine have beneficial effects on interstitial lung disease in SSc?	There is insufficient evidence for the use of azathioprine in SSc-ILD
Anti-CD20 therapy (Rituximab) 1. Do anti-CD20 therapies (rituximab) have beneficial effects on skin fibrosis in SSc? 2. Do anti-CD20 therapies (rituximab) have beneficial effects on interstitial lung disease in SSc?	Evidence from a pilot RCT, prospective open label studies and a case control study suggests beneficial effect on skin manifestations and ILD in SSc. More evidence is needed
TNF antagonists 1. Do TNF antagonists have beneficial effects on arthritis in SSc?	Evidence form retrospective studies suggest that TNF inhibitors may be beneficial in treatment of arthritis in SSc. More evidence is needed.before general recommendations can be given.
Tocilizumab 1. Does tocilizumab have beneficial effects on skin fibrosis in SSc? 2. Does tocilizumab have beneficial effects on interstitial lung disease in SSc? 3. Does tocilizumab have beneficial effects on musculoskeletal involvement (arthritis, myositis, tendinitis, contractures) in SSc?	Evidence from small observational study indicates that tocilizumab might have beneficial effect on arthritis. The results of a RCT evaluating tocilizumab in patients with diffuse SSc are awaited.*
Calcium channel blockers 1. Do calcium channel blockers have beneficial effects on digital ulcers in SSc?	Evidence from 2 small RCTs suggests that nifedipine may have beneficial effect for healing of digital ulcers. The efficacy of nifedipine and possibly other calcium channel blockers for treatment of digital ulcers in SSc should be further investigated in RCT.
ACE-inhibitors 1. Do ACE-inhibitors prevent scleroderma renal crisis?	There is no evidence that ACE inhibitors prevent scleroderma renal crisis.
Angiotensin receptor antagonist (Sartans) 1. Do sartans prevent scleroderma renal crisis? 2. Do sartans improve scleroderma renal crisis?	There is no evidence that sartans prevent scleroderma renal crisis. There is insufficient evidence that sartans improve scleroderma renal crisis.
Statins 1. Do statins prevent digital ulcers in SSc? 2. Do statins heal digital ulcers in SSc?	One RCT indicates that atorvastatin may prevent development of new digital ulcers in patients with SSc. There is insufficient evidence that statins improve healing of digital ulcers in SSc. Potential bias form co-medications cannot be excluded. The efficacy of statins in the treatment of

	digital ulcers in SSc needs further evaluation in RCT.
Prostacyclins 1. Do prostacyclin analogues improve scleroderma renal crisis in SSc?	There is insufficient evidence that prostacyklin analogues improve scleroderma renal crisis.
Endothelin receptor antagonists 1. Do endothelin receptor antagonists have beneficial effects on Raynaud's phenomenon in SSc?	There is insufficient evidence that endothelin receptor antagonists have beneficial effect on attacks of Raynaud's phenomenon in SSc.
Selective PDE-5 inhibitors 1. Do selective PDE-5 inhibitors have beneficial effects on erectile dysfunction in SSc?	Evidence form small open-label study suggests that tadalafil may improve erectile dysfunction in SSc.The efficacy of PDE-5 inhibitors in erectile dysfunction in SSc patients should be further evaluated in RCT
Anti-platelet aggregant/ anti-coagulant 1. Do anti-platelet drugs have beneficial effects on digital ulcers in SSc?	There is insufficient evidence that anti-platelet drugs have beneficial effect on digital ulcers in SSc
Non steroidal anti-inflammatory drugs (NSAIDs) 1. Do NSAIDs increase the risk of scleroderma renal crisis in SSc?	There is no evidence that NSAIDs increase risk of scleroderma renal crisis. In view of well recognized renal toxicity of NSAIDs experts believe that NSAIDs should be used with caution in SSc patients at risk of scleroderma renal crisis.
Other treatments 1. Does hydroxychloroquine have beneficial effects on arthritis in SSc?	There is no evidence that hydroxychloroquine has beneficial effect on arthritis in SSc.
General questions 1. Does local wound care have beneficial effects on digital ulcers in SSc?	Evidence concerning efficacy of local wound care in SSc patients is scarce. Experts think that local wound care is important for treatment of digital ulcers in SSc patients.
2. Does lymph drainage have beneficial effects on hand function in systemic sclerosis?	Results of 2 open-label RCT indicate that connective tissue massage and manual lymphatic drainage improve hand function in SSc. Experts appreciate the role of non-pharmacological treatment in SSc. The efficacy of connective tissue massage and manual lymphatic drainage should be further investigated in RCT.

ACE=angiotensin converting enzyme, ILD=interstitial lung disease, PDE=phosphodiesterase, RCT=randomized controlled trial, SSc=systemic sclerosis, SSc-ILD=SSc-related interstitial lung disease, TNF-tumor necrosis factor.

*See also information included in table S4 addressing the results of RCT published after closure of the systematic review.

SUPPLEMENTARY DISCUSSION

Table S4. Double-blind, randomized clinical trials evaluating new therapies in SSc patients published since the end of the literature analyses

Reference	Inclusion criteria (Number of SSc patients)	Treatment	Main findings
Hachulla, E., et al., Ann Rheum Dis, 2015.	SSc patients with DUs (n=83)	Sildenafil p.o. 20 mg three times daily versus placebo for 12 weeks	Primary endpoint: Non-significant trend toward reduction of time to healing for each DU in favor of sildenafil in ITT population (HR = 1.33; 95% CI 0.88 to 2.00; p=0.18) and in PPP population (1.49 95% CI 0.98 to 2.28, p=0.06) Secondary endpoints: Reduction of the mean number of DUs per patient in the sildenafil group compared with the placebo group at week 8 (1.23±1.61 vs 1.79±2.40, p=0.04) and week 12 (0.86±1.62 vs 1.51±2.68, p=0.01) No significant difference between sildenafil and placebo in other endpoints in ITT population
Khanna D, et al. Lancet 2016	dSSc with mRSS 15-40, disease duration </= 5 years since first non-Raynaud's symptom and: documentation of progressive skin disease or tendon friction rub and elevated acute phase reactants (n=87)	Tocilizumab s.c. 162 mg weekly versus placebo for 48 weeks	Primary endpoint: Non-significant trend toward skin score improvement in tocilizumab group compared with placebo at 24 weeks (mean treatment difference –2.70; 95% CI –5.85 to 0.45; p=0,0915) and 48 weeks (-3.55; 95% CI −7.23 to 0.12; p=0.0579) Secondary endpoints: Fewer patients in the tocilizumab group than in the placebo group had a decline in percent predicted FVC at 48 weeks (p=0.0373) No significant difference between tocilizumab and placebo in other endpoints
Khanna D, et al. JAMA 2016	SSc patients with DU (n=554: 289 in DUAL-1 and 265 in DUAL-2 study)	Macitentan p.o.. 3 mg/d or 10 mg/d versus placebo for 16 weeks	Primary endpoint: No significant difference between macitentan and placebo in the mean number of new digital ulcers per patient

dSSc=diffuse cutaneous SSc, DUs=digital ulcers, ITT = intention to treat, p.o.= orally, PPP = per protocol, s.c. = subcutaneously, SSc=systemic sclerosis.

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