



# REVISTA BRASILEIRA DE REUMATOLOGIA

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## Recommendations of the Brazilian Society of Rheumatology

### Recommendations for the management and treatment of systemic sclerosis<sup>☆</sup>

### Recomendações sobre diagnóstico e tratamento da esclerose sistêmica

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#### Description of the method to elaborate the evidence

The members of the Comissão de Esclerose Sistêmica da Sociedade Brasileira de Reumatologia (Systemic Sclerosis Commission of the Brazilian Society of Rheumatology, SBR) 2010-2012 took part in the Evidence Preparation Course given by the Associação Médica Brasileira (Brazilian Medical Association, AMB) in São Paulo in the first semester of 2011. The questions were formulated and discussed via internet in the second semester of 2011. The 15 clinical questions considered to be relevant were structured using the P.I.C.O. method (patient; intervention or indicator; comparison; outcome). The literature search was conducted by searching the data-

bases MEDLINE, EMBASE, SciElo/Lilacs, and the Cochrane Library through February, 2012 (Appendix). Critical assessment of the evidence in the selected articles was performed using the Jadad score. The observational studies and case series were considered for analysis when randomised clinical trials could not be located. A manual search located the relevant studies that were included in the analysis. The answers to the questions included in the Recommendations were refined and elaborated, and all of the selected references exhibited the corresponding grade of recommendation and the strength of scientific evidence. The references were updated through December, 2012, entered into a single file by the coordinator, and sent to the co-authors in four successive rounds for preparation of the final version.

<sup>☆</sup> Study with the seal of the Brazilian Society of Rheumatology.

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### Grades of recommendation and strength of evidence

- A:** Most consistent experimental and observational studies.
- B:** Less consistent experimental and observational studies.
- C:** Case reports (uncontrolled studies).
- D:** Opinion that is not substantiated by critical evaluation, based on consensus, physiological studies or animal models.

### Objective

To establish recommendations for the management and treatment of systemic sclerosis.

## Introduction

Systemic sclerosis (SSc), which is a chronic disease, affects the connective tissue and is characterised by manifestations derived from the fibrosis and dysfunction of the skin and internal organs. Its prevalence varies from 20 to 300 cases per one million adults. In 1980, the American College of Rheumatology (ACR) formulated the classification criteria for identifying patients with the well-established disease,<sup>1</sup> which is classified to be in limited or diffuse clinical form.<sup>2</sup> In the 21<sup>st</sup> century, the scope of SSc was enhanced after the formulation of novel criteria for SSc sine scleroderma,<sup>3</sup> early SSc,<sup>4</sup> and very early SSc,<sup>5</sup> which allow for the early diagnosis of a significant number of patients.

SSc manifests a wide scope of skin (fibrosis and calcinosis), vascular (Raynaud's phenomenon and ischaemic ulcers), and visceral characteristics (oesophageal and intestinal dysmotility, gastroesophageal reflux, interstitial lung disease (ILD), pulmonary hypertension (PH), scleroderma renal crisis, myocardial sclerosis, and heart arrhythmias).<sup>6</sup> Nailfold capillaroscopy<sup>7</sup> and specific autoantibodies<sup>8</sup> are also important tools for diagnosing and planning treatment. Of note, the treatment of SSc is based on organ-specific strategies because the various clinical manifestations might require different and specific medications.

### 1. What are the classification criteria for systemic sclerosis?

Several classification criteria were formulated for the stratification of SSc<sup>9</sup> (A).

The classification criteria most widely used in everyday clinical practice are the ones formulated in 1980 by the American Rheumatism Association (ARA), currently ACR (American College of Rheumatology)<sup>1</sup> (D). Targeting the first criteria with external validation, they established a pattern of disease definition that enables comparisons among groups of patients who are treated in different centres. Patients with SSc are thus classified when they meet the one major criterion or two or more of the minor criteria:

- Major criterion: proximal scleroderma (skin symmetric fibrosis proximal to the metacarpophalangeal or metatarsophalangeal joints).
- Minor criteria:
  - Sclerodactyly;

- Digital pitting or scars or loss of substance from digital finger pads (pulp loss); and
- Bibasilar pulmonary fibrosis on chest x-rays.

Following the criteria of LeRoy et al.,<sup>3</sup> SSc is classified into two subsets. Diffuse cutaneous SSc (dcSSc) is defined by the onset of Raynaud's phenomenon within 1 year of the appearance of skin changes that quickly progress with truncal and acral skin involvement, presence of tendon friction rubs, and early visceral infection (lung fibrosis, SRC, diffuse gastrointestinal disease, and myocardial sclerosis). In turn, the patients with limited cutaneous SSc (lcSSc) might exhibit Raynaud's phenomenon for years, slow-progressing skin infection restricted to the limbs (below the elbow and knees) and the face, or absent, significant late incidence of pulmonary artery hypertension (PAH), calcinosis, telangiectasia, and a high incidence of anti-centromere antibodies (ACA)<sup>2</sup> (B). The prevalence of dcSSc, lcSSc, and SSc, combined with another connective tissue disorder, was observed to be 36.9%, 57.5%, and 5.6%, respectively<sup>10</sup> (B).

A recent assessment of SSc-specific antibodies showed differential distribution parallel to the LeRoy's subsets of disease: ACA were detected in 46.7% of the patients classified as lcSSc versus 6% in the those classified as dcSSc, and the anti-topoisomerase I antibodies (anti-Scl-70) were detected in 23.4% of the patients classified as lcSSc versus 60.8% of the those classified as dcSSc<sup>6</sup> (B).

The criteria for the diagnosis of SSc sine scleroderma (ssSSc) were formulated in 2000. In this infrequent variety, the specific visceral infection is not attended by skin involvement. Clinically, ssSSc is characterised by the presence of objective Raynaud's phenomenon, positive anti-nuclear factor, and at least one organ exhibiting SSc specific infections, such as distal oesophageal hypomotility, small-bowel hypomotility, ILD, primary PH, myocardial sclerosis, or SRC<sup>3</sup> (B).

In 2001, LeRoy and Medsger formulated the criteria for early SSc that allow for the classification of patients in the early stages of SSc before the appearance of the typical skin or visceral manifestations and based on the following:

- Objective evidence of Raynaud's phenomenon (observed by the doctor) and scleroderma pattern of microangiopathy on nailfold capillaroscopy (NFC) or SSc-specific autoantibodies (ACA, anti-Scl-70, anti-RNA polymerase III) or
- Subjective evidence of Raynaud's phenomenon (reported in the clinical interview but not observed by the doctor) and scleroderma pattern of microangiopathy on NFC and SSc-specific autoantibodies<sup>4</sup> (B).

In several cases, the criteria for early SSc and ssSSc overlap. Whether ssSSc should to be included within the scope of lcSSc with a limited cutaneous involvement or whether ssSSc should be considered to be a distinct condition is a subject of current debate.

Finally, the European League Against Rheumatism (EULAR) and the EULAR Scleroderma Trial and Research (EUSTAR) group formulated non-validated classification criteria for very early SSc that include laboratory tests and NFC. The presence of Raynaud's phenomenon, finger swelling, and positive ANF indicate the need to investigate the specific antibodies (ACA

and anti-Scl-70) and to perform NFC. The presence of positive specific antibodies or the presence of scleroderma pattern on NFC leads to the classification of very early SSc and indicates the need to investigate visceral involvement<sup>8</sup> (B).

### Recommendation 1

Classification of SSc in limited and diffuse subsets best reflects the natural history of the disease and exhibits clear clinical differences. Positive-specific antibodies (anti-centromere and anti-Scl-70) and the scleroderma pattern of microangiopathy on NFC are reliable confirmatory criteria of SSc in the very early stage of the disease.

## 2. What is the role of nailfold capillaroscopy in the early diagnosis and follow-up of systemic sclerosis?

NFC allows for the early differential diagnosis between individuals with primary and secondary Raynaud's phenomenon. The scleroderma pattern of microangiopathy on NFC exhibits a high correlation with progression into SSc ( $P = 0.00001$ , 94% sensitivity, 92% specificity, 52% positive-predictive value, 99% negative-predictive value [odds ratio (OR), 163; 95% confidence interval (CI), 97.89-271.47])<sup>11,12</sup> (A). The presence of antinuclear antibodies (ANA) has a prognostic impact (hazard ratio (HR), 9.70) when it is associated with the scleroderma pattern of microangiopathy in patients with primary Raynaud's progressing into SSc<sup>13</sup> (A).

The early appearance of dilated megacapillaries and microhemorrhages on NFC is of paramount importance in the early diagnosis of SSc. These findings are more frequent in the active stage of the disease, whereas the presence of areas with capillary devascularisation, destructurement of the capillary bed architecture, and the presence of branching capillary loops and bushy loops correspond to the vascular damage associated with the advanced stages of SSc<sup>14</sup> (A).

NFC might be performed using different types of equipment, including stereomicroscopes, video-capillaroscopes, and dermatoscopes<sup>7</sup> (A). The former two are considered to exhibit better sensitivity and accuracy in the assessment of the peripheral microangiopathy associated with the scleroderma pattern<sup>13</sup> (A). One study found satisfactory accuracy in the assessment of the nailfold capillaries using dermatoscopy, with 83.1% sensitivity and 100% specificity in the diagnosis of SSc<sup>15</sup> (A).

According to several studies, there is a correlation between changes in NFC and risk of finger ulcers. The reproducibility of the capillaroscopic skin ulcer risk index (CSURI) has been validated. This index is calculated using the equation:  $D \times M/N^2$ , where D is the maximum loop diameter of megacapillaries, M is the number of megacapillaries (diameter  $\geq 50 \mu\text{m}$ ), and N is the total number of capillaries in the distal row. This index was found to be highly predictive of the appearance of digital ulcers in SSc 3 months after assessment using a videocapillaroscopy (92.9% sensitivity [95% CI, 83.0-98.0]; 81.4% specificity [95% CI, 74.8-86.8]; cut-off point: 2.96, and area under receiver operator characteristic (ROC) curve: 0.884 [95% CI, 0.835-0.922])<sup>16,17</sup> (A).

NFC is also considered to be useful for assessing the severity of SSc. In patients with SSc for  $\leq 5$  years, a study found a positive correlation between the capillaroscopic changes observed using a stereomicroscopy and the presence of ground-glass infiltrates on high-resolution chest tomography, thus suggesting that NFC might be useful in the identification of predictors of lung involvement<sup>18</sup> (A). A similar correlation was found relative to the degree of involvement of other target organs (digestive system, kidney, and musculoskeletal system) [ $P < 0.01$ ]<sup>19</sup> (A).

### Recommendation 2

NFC allows for the early diagnosis of SSc and is useful for assessing its severity and prognosis.

## 3. What is the role of autoantibodies in the early diagnosis and follow-up of patients with systemic sclerosis?

The detection and quantification of specific antibodies became significant tools for the diagnosis, classification, and prognosis of SSc<sup>10</sup> (B).

### SSc-specific antibodies

#### Anti-centromere antibodies

Anti-centromere antibodies (ACA) are detected in 60-82% of the patients with lcSSc and in 2-7% of the patients with dcSSc<sup>6</sup> (B). A specific pattern on indirect immunofluorescence (IFI) using HEp-2 cells allows for the identification of ACA<sup>20,21</sup> (B).

ACA-positive patients exhibit longer latency period (average,  $6.5 \pm 10$  years) before the first manifestation, in addition to Raynaud's phenomenon, compared to the patients with anti-Scl-70 antibodies (average,  $2.4 \pm 5.6$  years). For this reason, the diagnosis might be delayed in many cases<sup>6,22</sup> (B).

Several studies reported an association between positive ACA and the presence of calcinosis, PAH, and finger ulcers<sup>6,22</sup> (B).

#### Anti-DNA topoisomerase I antibodies

The sensitivity of anti-DNA topoisomerase I antibodies (anti-Scl-70), which are assessed using double immunodiffusion or immunoblot, is variable because they are detected in 26-76% of the patients, with a specificity of 98-99.6%<sup>6,23,24</sup> (B). They might be detected in 40-70% of the patients with dcSSc and 36% of the patients with lcSSc<sup>6,23</sup> (B). The presence of anti-Scl-70 is associated with a higher prevalence of faster skin and visceral infection, myositis, lung fibrosis, and pericarditis<sup>24</sup> (B).

### Other autoantibodies associated with SSc

#### Anti-RNA polymerase

There are three types of RNA polymerase (I, II, and III). The presence of anti-RNA polymerase I/II/III antibodies is associated with dcSSc (77.8%; other groups, 12.4%;  $P < 0.001$ ; relative risk (RR), 6.3). Anti-RNA polymerase I and II-positive patients also exhibit a higher incidence of dcSSc, however, without statistical significance (dcSSc, 42.9%; other groups, 15.7%)<sup>25</sup> (B).

Anti-RNA polymerase-positive patients exhibit a significantly higher incidence of kidney involvement (29.0%; other, 11.3%;  $P < 0.05$ ; RR, 2.6), and the probability of kidney disease of anti-RNA polymerase I/II/III-positive patients is 40%<sup>25</sup> (B).

#### Anti-U3RNP (fibrillar) antibodies

These antibodies are more frequently detected in younger, male, and black patients. The presence of anti-fibrillar antibodies bears a correlation with dcSSc and occurs in  $< 10\%$  of the patients with SS<sup>c</sup><sup>26,27</sup> (B).

#### Anti-Th/To antibodies

These antibodies bear a correlation with poor prognostic lc-SSc and more severe ILD and PH<sup>8,28</sup> (D).

### Recommendation 3

The investigation of specific autoantibodies helps in the diagnosis of SS<sup>c</sup>. Anti-centromere antibodies are classically associated with the limited form of the disease, whereas anti-Scl-70 is strongly associated with diffuse SS<sup>c</sup> and has significant prognostic value (faster skin and visceral involvement, myositis, lung fibrosis, and pericarditis). Anti-RNA polymerase autoantibodies are associated with the diffuse form of the disease and kidney involvement.

## 4. What treatments are beneficial for skin thickening in systemic sclerosis?

The modified Rodnan total skin score (MRTSS) assesses skin thickness by palpation of 17 body sites (fingers, back of the hands, arms, forearms, feet, legs, thighs, face, chest, and abdomen) on a scale varying from 0 to 3, where 0 = normal, 1 = mild thickness, 2 = moderate thickness, and 3 = severe thickness. The MRTSS varies from 0 (no thickness) to 51 (severe thickness in all 17 sites)<sup>29</sup> (B). Skin thickness might also be assessed using a hand-held digital durometer that measures the hardness of the skin at six body sites (forearms, thighs, and legs) on a continuous scale. The total score is derived from the sum of the average measure of the six investigated sites<sup>30</sup> (B).

Two clinical studies investigated the effect of methotrexate on the skin component of SS<sup>c</sup>. One study assessed the effect of methotrexate per intramuscular (IM) route in the dose of 15 mg per week, eventually increased to 25 mg per week in 29 patients with SS<sup>c</sup> for  $> 3$  years, and skin thickening or persistent finger ulcers in the last 6 months. After 24 weeks of treatment, 68% of the volunteers exhibited  $\geq 30\%$  improvement in the total skin score, which corresponded to the sum of the skin thickness scores in 26 body sites on a scale of 0 to 4 scale (original Rodnan score)<sup>31</sup> (B). The other study assessed treatment with methotrexate, 10 mg per week, over 2 months (increasing to 15 mg per week) in 71 patients with SS<sup>c</sup> and a minimum of 5 points on the UCLA score. The results showed that treatment with methotrexate induced a significant reduction of 22.5% in the MRTSS and 20% in the UCLA score compared to the untreated group after a 12-month follow-up<sup>32</sup> (A).

Patients with SS<sup>c</sup> and treated with D-penicillamine (250 mg/day or 125 mg on alternate days) on a daily basis (increasing from one capsule in the two first months to two capsules

on months 3 and 4, three capsules on months 5 to 7 and four capsules on the ensuing months, totalling 1,000 mg in the first group) over 24 months exhibited the same results on MRTSS with either dose (score reduction of  $4.8 \pm 10.3$  with the high dose, and  $6.9 \pm 8.4$  with the low dose)<sup>33</sup> (A). As a function of that similarity of the results of the high and low (considered to act as a placebo) doses and the high index of side effects associated with the use of D-penicillamine, most rheumatologists stopped prescribing this drug in the last decade.

Recombinant human relaxin in doses of 25 mg/kg/day or 100 mg/kg/day as continuous subcutaneous (SC) infusion was tested in patients with SS<sup>c</sup> for  $> 5$  years and MRTSS of at least 20 compared to no treatment over 24 weeks. The lower tested dose of 25 mg/kg/day reduced the skin score compared to the untreated volunteers (reduction of 23.6%, 27.5%, and 28.7% during weeks 4, 12, and 24, respectively), whereas the volunteers who received 100 mg/kg/day did not exhibit any benefit when compared to the untreated patients<sup>34</sup> (A) and MRTSS was similar in the treated and untreated groups during weeks 4, 12, and 24. The discontinuation of relaxin during week 24 induced severe side effects with kidney infection manifested as reduced creatinine clearance and renal crisis, or grade 3 or 4 arterial hypertension<sup>35</sup> (A). Because the recombinant human relaxin was not shown to be better than placebo relative to the skin and visceral manifestations of dcSS<sup>c</sup> and its discontinuation was associated with severe renal side effects, relaxin was not indicated for the treatment of SS<sup>c</sup>.

In patients with SS<sup>c</sup> and MRTSS of  $\geq 16$ , treatment using oral type I collagen in a dose of 500  $\mu\text{g}/\text{day}$  over 12 months was not associated with changes in the score. Nevertheless, an analysis of the subgroup of patients who exhibited SS<sup>c</sup> for 3 to 10 years showed a significant score reduction ( $7.9$  vs.  $2.9$ )<sup>36</sup> (A). The use of collagen as antifibrotic medication provides a satisfactory therapeutic perspective that must still be more properly investigated.

The use of intravenous (IV) infusions of iloprost in doses of 0.5 ng/kg/min or 2 ng/kg/min once per day over 21 days did not induce MRTSS changes in patients with SS<sup>c</sup> after 1 year of follow-up<sup>37</sup> (B).

A double-blind, randomised, placebo-controlled trial using oral cyclophosphamide on a daily basis in 158 patients and whose primary outcome was the drug effect on ILD observed a significant improvement ( $P < 0.01$ ) of the skin score after 12 months and 24 months of follow-up. Improvement disappeared after drug discontinuation<sup>38</sup> (A) and was more significant in the patients with dcSS<sup>c</sup><sup>39</sup> (A).

An open-label study that assessed 25 treatment-naïve patients with recent SS<sup>c</sup> ( $< 24$  months) using mycophenolate mofetil (average dose, 2.0 g/day; average length of use,  $18.2 \pm 8.7$  months) reported significant improvement in the MRTSS (from  $24.5 \pm 8.6$  at baseline to  $14.5 \pm 10.9$  at the end of treatment) and affected skin area (from  $36 \pm 16\%$  to  $14 \pm 13.3\%$ ) in 15 patients who completed the study. The results of the lung function test remained stable throughout the study, and the skin biopsy of three patients exhibited a remarkable reduction of the collagen fibre accumulation<sup>40</sup> (B).

Following 1 year of treatment with rituximab (375 mg/m<sup>2</sup>), the MRTSS of patients with SS<sup>c</sup> and ILD exhibited reductions of 5.13 and 8.65 at 1 and 2 years of follow-up, respectively. The percentage of improvement using rituximab was 18.45%<sup>41,42</sup> (A).

An open-label phase IIa study assessing imatinib mesylate in a dose of 400 mg/day in 30 patients with dcSSc over 12 months demonstrated a reduction of MRTSS (6.6 points or 22.4%) at the end of treatment for 24 patients who completed the study. The improvement was more evident after 6 months of treatment, in both the patients with recent and late-phase disease<sup>43</sup> (B). A total of 171 adverse events were observed, of which 24 were severe.

Another open-label phase I/IIa study that assessed 20 patients with SSc and active ILD using imatinib mesylate showed an average reduction of 3.9 points in the MRTSS (baseline 18.7 ± 10.1) of the 12 patients who completed the study ( $P < 0.001$ )<sup>44</sup> (B). Seven patients did not complete the study due to side effects. Common side effects, such as fatigue, face swelling, nausea and vomiting, diarrhoea, generalised rash, and proteinuria, occurred in > 20% of the volunteers and are associated with doses of > 600 mg/day.

#### Recommendation 4

Methotrexate is the first drug of choice for progressive skin thickening in patients with SSc. Cyclophosphamide, mycophenolate mofetil, and rituximab might represent options for the patients who do not respond to methotrexate.

## 5. What treatments are beneficial for subcutaneous calcinosis in systemic sclerosis?

### Pharmacological treatment

The data on the effect of warfarin for the treatment of calcinosis in patients with SSc are conflicting. Although three studies reported improvement of calcinosis with the use of low doses (1 mg/day; 12-18 months)<sup>45-47</sup> (C), a fourth study did not find that treatment effective<sup>48</sup> (C). Treatment with warfarin is more effective in patients at the early stages of calcinosis. No study using low doses reported increased bleeding or changes in the coagulation time.

The patients with lcSSc who used diltiazem in a dose of 240-480 mg/day for 1 or 2 years had reduced or improved calcinosis with consequent clinical benefits<sup>49</sup> (C). A lower dose (180 mg/day) was not able to induce a similar clinical response but only slight radiological improvement<sup>50</sup> (C).

In patients with SSc and calcinosis, cycles of minocycline (50 or 100 mg/day) (treatment over 4 to 8 weeks, followed by interruption over 3 to 4 months) reduced ulcers and inflammation but induced a slight reduction of calcinosis<sup>51</sup> (C).

Colchicine per oral route in a dose of 1 mg/day over 3 months improved the healing of ulcers and reduced the associated inflammation in patients with SSc and calcinosis<sup>52</sup> (C).

Other agents, such as bisphosphonates (risedronate), IV immunoglobulin, and rituximab, were associated with reduced calcinosis in several patients with lcSSc, as demonstrated in the results of case reports<sup>53</sup> (C).

### Non-pharmacological treatment

Surgery should be taken into consideration as an option after several instances of therapeutic failure, provided calcifica-

tions are well delimited because surgery increases the risk of infection and skin necrosis<sup>54</sup> (C).

Carbon dioxide laser (CO<sub>2</sub> laser) might be used to “vaporise” superficial calcinosis in patients with CREST syndrome (calcinosis, Raynaud’s, oesophageal dysmotility, sclerodactyly, and telangiectasia)<sup>55</sup> (C).

Extracorporeal shock wave lithotripsy (ESWL), which might be effective, is associated with low morbidity in patients with CREST syndrome and ulcerated calcinosis, thus reducing the number of calcifications and the size of ulcerations<sup>56</sup> (C).

#### Recommendation 5

Warfarin might be effective in the early stage of calcinosis, and diltiazem might reduce or improve calcinosis, whereas minocycline and colchicine improve the healing of ulcerations and the inflammation that is associated with calcinosis. No treatment proved to be entirely effective against calcinosis in SSc.

## 6. What treatments are beneficial for Raynaud’s phenomenon in systemic sclerosis?

### Calcium-channel blockers

Calcium-channel blockers, dihydropyridines in particular, are efficacious in the treatment of Raynaud’s phenomenon secondary to SSc.<sup>57</sup> The calcium-channel blockers reportedly reduced the number (*weighted mean difference* [WMD], -8.31; 95% CI, -15.71 to -0.91;  $P = 0.03$ ) and the severity of ischaemic episodes by 35% (*standard mean difference* [SMD], -0.69; 95% CI, -1.21 to -0.17;  $P = 0.01$ ) in up to 2 weeks of treatment. Nifedipine in a dose of 10-20 mg three times per day has shown to reduce the number of ischaemic episodes (WMD, -10.21; 95% CI, -20.09 to -0.34;  $P = 0.04$ ) after 2 to 12 weeks of treatment<sup>57</sup> (B). Nifedipine is the first drug of choice to treat Raynaud’s phenomenon in patients with SSc.

In a randomised clinical trial, nicardipine did not induce a statistically significant ( $P > 0.05$ ) reduction of the frequency and severity of ischaemic episodes<sup>58</sup> (B).

Compared to placebo, diltiazem did not show efficacy in the reduction of the frequency or severity of Raynaud’s phenomenon in a clinical study<sup>59</sup> (B). Despite the lack of controlled clinical studies, amlodipine might represent an alternative to nifedipine in the treatment of Raynaud’s phenomenon<sup>60</sup> (D).

### Prostacyclin analogues

One randomised, placebo-controlled trial showed that IV iloprost in a dose of 0.5-2 ng/kg/min over 6 hours for 5 consecutive days reduced the average number (39.1-22.2%;  $P = 0.005$ ) and severity (34.8-19%;  $P = 0.01$ ) of ischaemic episodes in 9 weeks<sup>61</sup> (B). After 3 months, treatment with a low dose (0.5 ng/kg/min) of IV iloprost infused over 6 hours proved to be as efficacious as the higher doses (maximum-tolerated dose of 2 ng/kg/min). Both regimens reduced the frequency (40%) and length (30%) of Raynaud’s phenomenon up to 1 week after the end of treatment<sup>37</sup> (B). However, iloprost is not marketed in Brazil, and the consequent unfavourable cost/benefit ratio

limits its indication for patients with severe Raynaud's phenomenon associated with SSc.

Oral iloprost in a 50- $\mu$ g dose twice per day over 6 weeks did not reduce the length, frequency, or severity of ischaemic episodes at 6 and 12 months ( $P > 0.05$  in all the outcomes)<sup>62</sup> (B).

Intravenous iloprost (2 ng/kg/min over 8 hours for 3 to 5 consecutive days, and subsequently once per day every 6 to 8 weeks) proved to be slightly better ( $P = 0.04$ ) compared to nifedipine (30-60 mg/day) to control Raynaud's phenomenon in patients with SSc<sup>63,64</sup> (B).

The side effects related with iloprost were nausea and vomiting (83%), jaw pain (69%), muscle pain (34%), diarrhoea (28%), and chills (17%). Tachycardia was reported in 6% of the patients using nifedipine<sup>63,64</sup> (B).

### Alpha-adrenergic blockers

Two studies that used prazosin for the treatment of Raynaud's phenomenon showed modest results<sup>65</sup> (A). In another study with a larger number of patients ( $n = 20$ ), prazosin administered orally (3 mg/day over 8 weeks) induced a reduction of the weekly Raynaud's phenomenon attack frequency (mean difference [MD], -3.5; 95% CI, -5.85 to -1.15), and a side effect rate of 18%<sup>66</sup> (B).

### Endothelin receptor antagonists

Bosentan, an oral endothelin receptor antagonist (ERA), in a dose of 62.5 mg twice per day over 4 weeks followed by 125 mg twice per day over 12 weeks, did not improve the frequency, length, associated pain, or severity of Raynaud's phenomenon attacks in patients with SSc and Raynaud's without pre-existing finger ulcers ( $P > 0.05$ )<sup>67</sup> (B).

### Angiotensin I-converting enzyme (ACE) inhibitors and angiotensin II-receptor antagonists

Quinapril in a dose of 80 mg/day or in the maximum-tolerated dose did not reduce the frequency (MD, 0.3; 95% CI, -5.6 to 6.3) and the severity (MD, 0.1; 95% CI, -6.1 to 6.3) of Raynaud's attacks<sup>68</sup> (B).

Losartan (50 mg/day) did not induce a significant difference in the frequency and the severity of the attacks of Raynaud's phenomenon secondary to SSc at 3 and 15 weeks compared to nifedipine (40 mg/day) ( $P > 0.05$ )<sup>69</sup> (B).

### Phosphodiesterase inhibitors

One clinical study using tadalafil in a dose of 20 mg on alternate days over 6 weeks in a small number of patients with SSc or mixed connective tissue disease (MCTD) using calcium-channel blockers (72% also using other vasodilators) reported a reduction of the frequency (2.29 vs. 3.37;  $P = 0.0004$ ), duration (34 min vs. 55 min;  $P = 0.02$ ), and severity ( $P < 0.0005$ ) of the Raynaud's phenomenon episodes<sup>70</sup> (B). Another clinical study using tadalafil as monotherapy in a dose of 20 mg/day over 4 weeks in women with Raynaud's secondary to SSc did not find a reduction of the frequency ( $P = NS$ ), duration ( $P = NS$ ), or severity ( $P = NS$ ) of the ischaemic episodes<sup>71</sup> (B).

An analysis of clinical trials with small numbers of volunteers, open-label studies, and case reports assessing sildenafil demonstrated reductions of the severity and number of Raynaud's attacks in patients with SSc<sup>72</sup> (D).

The use of extended-release sildenafil in a dose of 100 mg/day over 3 days followed by 200 mg/day over 25 days in patients with Raynaud's phenomenon secondary to lcSSc reduced the weekly frequency of the episodes (44% vs. 18.1%;  $P = 0.034$ ) but did not reduce their duration nor the associated pain ( $P = NS$ )<sup>73</sup> (B). Although the extended-release sildenafil is a good option for patients with SSc who are unresponsive to calcium-channel blockers, sildenafil is not marketed in Brazil.

### Other drugs

Cyclofenyl is not effective in the treatment of Raynaud's phenomenon secondary to SSc<sup>74</sup> (B).

Ketanserin did not reduce the frequency [(fixed) MD, 25.20 (95% IC 22.55, 27.85)] and the duration [(fixed) MD, 4.10 (95% CI, 3.57, 4.63)] of Raynaud's phenomenon secondary to SSc<sup>75</sup> (A).

Compared to placebo, atorvastatin did not improve the severity of Raynaud's phenomenon secondary to SSc (MD, -0.8; 95% CI, -2.52 to 0.92;  $P = 0.35$ )<sup>76</sup> (B).

The use of antioxidants (selenium, beta-carotene, vitamin E, vitamin C, and methionine associated with allopurinol) did not reduce the number and the duration of Raynaud's attacks in up to 10 weeks in patients with SSc<sup>77</sup> (B).

### Recommendation 6

Calcium-channel blockers might reduce the frequency and the severity of ischaemic episodes in patients with Raynaud's phenomenon secondary to SSc. They should be the first drugs of choice for the treatment of Raynaud's phenomenon in SSc.

Intravenous iloprost reduced the number and the severity of the ischaemic episodes. The low doses are as efficient as the higher doses in patients with Raynaud's phenomenon secondary to SSc. Iloprost is not marketed in Brazil.

The use of extended-release sildenafil reduces the frequency of attacks in patients with Raynaud's phenomenon secondary to SSc. Sildenafil is not available in Brazil.

## 7. What treatments are beneficial for ischaemic ulcers in systemic sclerosis?

### Prostacyclin analogues

Two randomised clinical trials demonstrated beneficial effects of IV iloprost in the treatment of ischaemic ulcers. In one study, iloprost in IV infusion (0.5-2 ng/kg/min) over 6 hours for 5 consecutive days) was associated with 85% increase in the number of patients with full healing of the finger skin ischaemic injury (ulcer, fissure, or paronychia) compared to placebo (number needed to treat, NNT= 1) in up to 10 weeks<sup>78</sup> (B). In the other study, the group that used iloprost exhibited 14.7% more patients with healing of at least 50% of the finger lesions in up to 3 months compared to the group that used placebo; this difference was not statistically significant ( $P = 0.06$ )<sup>61</sup> (B).

Iloprost per IV route did not reduce the number of patients who developed new lesions in up to 9 months (NNT = NS)<sup>61</sup> (B).

Treatment using IV iloprost over 6 hours in low dose (0.5 ng/kg/min) over 3 weeks was as efficient as the higher doses (maximum-tolerated dose of 2 ng/kg/min). Iloprost in high dose reduced by 76.2% and the low dose reduced by 61% the number of finger ulcers 1 week after the end of treatment. The reduction in the number of finger ulcers did not exhibit a significant difference between the high and low doses (P = NS)<sup>37</sup> (B).

A comparison of IV iloprost (0.5-2 ng/kg/min over 8 hours on 3 consecutive days, and one additional infusion in week 8) and nifedipine (30 mg/day increasing to 60 mg/day after 4 weeks over 12 weeks) demonstrated a reduction of the number of finger lesions (ulcers, fissures, and paronychia) in both groups, without a significant difference between the treatments in 16 weeks (MD, -0.8; 95% CI, -2.09 to 0.49, P = 0.20)<sup>64</sup> (B).

The use of alprostadil (prostaglandin E<sub>1</sub>) in IV infusion was associated with improvement of symptoms in 17 of 20 infusions performed in a total of 12 patients, and healing of 35 of 65 ischaemic ulcers between 2 and 6 weeks after the end of treatment, and the benefits persisted from 1 to 18 months<sup>79</sup> (C). A clinical study that compared the efficacy of iloprost and IV alprostadil in patients with Raynaud's phenomenon and finger ulcers reported significant improvement of ulcer healing in both groups<sup>80</sup> (B). Because iloprost is not marketed in Brazil, the IV infusion of alprostadil represents a therapeutic option for severe ischaemic ulcers refractory to conventional treatment.

#### Endothelin receptor antagonists

Bosentan was assessed in two randomised clinical trials including patients with SSC. In patients with SSC and at least one active finger ulcer, bosentan (62.5 mg PO twice per day during 4 weeks, and 125 mg twice per day for > 20 weeks) reduced the number of new finger ulcers by 30% compared to the placebo (mean ± standard error [SE], 1.9 ± 0.2 vs. 2.7 ± 0.3; P = 0.04) in up to 24 weeks. The investigated treatment did not influence the time needed for complete healing of all the existent (HR, 0.94; 95% CI, 0.65-1.37; P = 0.74) or new finger ulcers (HR, 1.40; 95% CI, 0.78-2.51; P = 0.26) in up to 24 weeks<sup>81,82</sup> (A).

#### Phosphodiesterase inhibitors

In a cross-over study with a small number of patients with SSC or MCTD using calcium-channel blockers (72% also using other vasodilators), tadalafil (20 mg on alternate days over 6 weeks) associated with healing of 100% of the finger lesions (ulcers or fissures) compared to 23% in the group that used placebo (P < 0.001, NNT = 2), and prevented the development of new ischaemic lesions in 92% of the patients (P = 0.001)<sup>70</sup> (B). Because the action of tadalafil as a single vasodilator in the treatment of ischaemic ulcers in SSC has not yet been assessed, its efficacy has not yet been established.

In an open-label study including 19 patients with SSC and finger ulcers refractory to conventional treatment, treatment with sildenafil (50-100 mg/day) was associated with a significant reduction of the number of ulcers after 6 months<sup>83</sup> (B).

#### Other medications

Atorvastatin (40 mg/day over 4 months) reduced the total number of finger ulcers (MD, -0.6; 95% CI, -1.15 to -0.04; P = 0.03), as well as the number of new ones (P = 0.003) compared to placebo after 4 months in a single clinical study<sup>76</sup> (B).

#### Recommendation 7

In patients with SSC, intravenous iloprost increases the number of healed active finger ulcers. The low doses are as efficacious as the higher doses. There is no difference in the reduction of the number of finger lesions between intravenous iloprost and nifedipine. Iloprost is not available in Brazil.

Due to the unavailability of iloprost in Brazil, intravenous alprostadil might represent an option for the treatment of severe ischaemic ulcers refractory to conventional treatment.

In patients with SSC, bosentan decreases the development of new finger ulcers.

The use of sildenafil might contribute toward reducing the number of finger ulcers.

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## 8. What are the maintenance treatments to prevent the recurrence of ischaemic ulcers in systemic sclerosis?

#### Endothelin receptor antagonists

Two randomised clinical trials that compared bosentan versus placebo demonstrated a significant reduction of the number of new finger ulcers in the group of patients with SSC treated with bosentan. One study included 122 patients with dcSSc or lcSSc and a previous history of finger ulcers; treatment with bosentan over 12 weeks reduced the number of new lesions by 48%, especially in the volunteers with diffuse disease and multiple finger ulcers [RAPIDS-1 study]<sup>81</sup> (A).

In the other study, patients with at least one active ischaemic finger ulcer treated with bosentan over 24 weeks exhibited a 30% reduction of the number of new lesions. The results were better in the patients with multiple finger ulcers [RAPIDS-2 study]<sup>82</sup> (A).

The recommended dose of bosentan is 62.5 mg twice per day for 1 month, and 125 mg twice per day from the second month onward. Adverse effects included increased transaminase levels (14-12.5%), diarrhoea (9%), peripheral swelling (18.8%), ventricular tachycardia, and pneumonia<sup>81,82</sup> (A).

#### Recommendation 8

Endothelin receptor antagonists, bosentan in particular, are recommended as treatment to prevent the recurrence of ischaemic ulcers.

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## 9. What treatments are beneficial for oesophageal and intestinal hypomotility in systemic sclerosis?

Metoclopramide improves the oesophageal lower sphincter pressure and the stomach emptying but it does not improve

the oesophageal motility<sup>84,85</sup> (C). Despite the lack of high-quality randomised clinical studies, metoclopramide and domperidone 30 min before meals is the standard maintenance treatment for patients with oesophageal hypomotility.

Long-term (6 months) use of long-acting octreotide, which is a somatostatin analogue, might improve the symptoms and quality of life for patients with SSc and small-bowel disease that are non-responsive to prokinetic agents<sup>86</sup> (C). A combination of octreotide with erythromycin might improve the symptoms associated with intestinal pseudo-obstruction (distension, abdominal pain, and nausea)<sup>87</sup> (C).

#### Recommendation 9

Prokinetic agents (metoclopramide, domperidone, and octreotide) should be used to relieve the symptoms associated with gastrointestinal dysmotility.

### 10. What treatments are beneficial for gastroesophageal reflux and its complications in systemic sclerosis?

Patients with SSc for an average of 6 years, who did not use medication and who exhibited oesophageal involvement of different stages of severity (stages I to IV), presented variable types of respiratory infections. Lung infection was 30-40% greater in the severe stages of oesophageal disease, including gastroesophageal reflux (GER) with progressive deterioration, and decline of the respiratory function after a 2-year follow-up<sup>88</sup> (B).

The treatment of SSc and history of GER accompanied by typical symptoms, such as heartburn or acid regurgitation with omeprazole 20 mg twice per day over 6 weeks, or omeprazole 20 mg combined with ranitidine 300 mg, resulted in increased quality of life scores and symptom relief with no difference between both regimens<sup>89,90</sup> (B).

The gastrointestinal system is one of the sites most often affected in SSc. Approximately 44% of the patients exhibit GER and 15% present with oesophageal dysmotility. Proton pump inhibitors (PPIs) might be used to improve the symptoms of GER and oesophagitis. Treatment with lansoprazole, 30 mg/day, is associated with improvement of symptoms (heartburn, regurgitation, and dysphagia) and increase in the frequency of diarrhoea after 6 months, and worsening of dysphagia after 12 months<sup>91</sup> (B).

Barrett's oesophagus is a complication of chronic GER that also appears in patients with SSc. During the 3-year follow-up of a population of such patients, high-grade dysplasia or oesophageal adenocarcinoma was diagnosed in 3% of the sample per year, and the incidence of adenocarcinoma exhibited a progressive increase in the patients with dysplasia<sup>92</sup> (B).

Patients with SSc and oesophageal complaints, mainly GER non-responsive to pharmacological treatment, might be subjected to several surgical procedures, including oesophagectomy, laparoscopic fundoplication with or without gastropasty, and laparoscopic Roux-en Y. Dysphagia decreased (0.42 versus 1.82), and reflux was better controlled after 2 years<sup>93</sup> (B). However, because the oesophageal problems might ex-

hibit late relapse in patients with SSc, surgery is not usually performed in individuals with scleroderma.

#### Recommendation 10

PPIs improve reflux oesophagitis, the symptoms of GER, and the local or respiratory complications. Surgery might be beneficial in the cases that are non-responsive to clinical treatment.

### 11. What treatments are beneficial for malabsorption syndrome in systemic sclerosis?

Oesophageal dysmotility and disorders of the intestinal function are remarkable manifestations of SSc and might exert significant effects on the nutrient absorption and nutritional state of patients. With regard to the nutrient intake, anthropometric measurements and biochemical nutritional state, individuals with SSc and gastrointestinal symptoms exhibit similar nutrient and energy intake but less consumption of fibre, vegetables, and fruits compared to healthy patients. The risk of malnutrition was found to increase by 50% in individuals with SSc<sup>94</sup> (B). Using the *Malnutrition Universal Screening Tool* (MUST), 18% of the individuals with SSc exhibited a high risk of malnutrition, which is associated with loss of appetite and abdominal distension<sup>95</sup> (B).

Open-label studies elaborated on the beneficial changes in antibiotic therapy, which no longer induced malabsorption symptoms, as shown by the normal results in the D-Xylose absorption test and the vitamin B<sub>12</sub> absorption in patients with SSc after antibiotic treatment. The patients exhibited increased appetite and weight gain, anaemia was corrected, and pain and abdominal distension decreased<sup>96,97</sup> (C).

In a study on a small number of patients with SSc and symptoms compatible with intestinal malabsorption non-responsive to prokinetic agents, the use of octreotide 0.1 mg per subcutaneous (SC) route twice per day or octreotide 20 mg/month per intramuscular (IM) route was shown to induce a significant reduction of the severity of symptoms after 6 months of treatment ( $0.7 \pm 0.5$ ,  $P = 0.003$ )<sup>96</sup> (C).

Parenteral nutrition might be beneficial in patients who exhibit signs of intestinal failure, bacterial overgrowth, malabsorption, and absence of response to antibiotics<sup>98</sup> (B).

One study assessed the effect of rifamycin (400 mg three times per day) over 10 days in patients with SSc and signs of small-bowel intestinal overgrowth and noted eradication of the abnormal bacterial concentration in 73.3% of the patients and improved symptoms in 72.7%<sup>99</sup> of the patients (B). Despite the lack of prospective randomised studies, antibiotic rotation (metronidazole, tetracycline, amoxicillin, and ciprofloxacin, preferentially) is usually recommended in patients who suffer from chronic diarrhoea due to bacterial overgrowth and who have SSc and blind loop syndrome.

#### Recommendation 11

The use of prokinetic agents, such as octreotide, reduces the severity of the symptoms associated with intestinal dysmotility.



Antibiotic rotation might eradicate the bacterial overgrowth.

Nutritional support (parenteral nutrition) might be beneficial in the most severe cases of malnutrition.

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## 12. What treatments are beneficial for interstitial lung disease in systemic sclerosis?

Among other autoimmune diseases, the fast progressing ILD might be treated with cyclophosphamide (six to nine IV cycles, 0.5 g/m<sup>2</sup> body surface) combined with prednisolone 50 mg followed by 5-7.5 mg/day as maintenance to improve the tolerance to exercise and lung function. The radiological findings at baseline remained stable after 10 months<sup>100</sup> (C).

Patients with SSc, restrictive lung disease, dyspnoea, and evidence of inflammatory ILD treated with cyclophosphamide PO ( $\leq 2$  mg/kg/day) over 2 years exhibited 2.5% improvement of the forced vital capacity (FVC) that persisted 24 months. The frequency of adverse events was higher in the patients treated with cyclophosphamide compared to the untreated patients, but there was no significant difference in the frequency of severe adverse events between both groups<sup>38</sup> (A).

Patients with SSc for  $14.2 \pm 8.3$  months and the presence of diffuse lung disease (ground-glass pattern) diagnosed using high-resolution computed tomography (CT) and deterioration of the FVC (forced vital capacity) and deterioration of the diffusion capacity of carbon monoxide (DLCO) can be treated with cyclophosphamide in monthly IV pulses (750-1,000 mg/m<sup>2</sup>) combined with 1 g of methylprednisolone, and between treatment, steroids in daily oral doses (methylprednisolone, 6 to 8 mg). After 6, 24, and 48 months of treatment, DLCO deteriorated in 23.1%, 33%, and 41.6% of the patients, improved in 15.3%, 16.6%, and 33.3% of the patients, and remained stable in 61.5%, 50%, and 25% of the patients, respectively. After 6, 12, 24, and 48 months of treatment, the FVC deteriorated in 15.3%, 23.0%, 33.3%, and 33.3% of the patients, improved in 7.6%, 15.3%, 16.6%, and 16.6%, and remained stable in 76.9%, 61.5%, 50.5%, and 50.0%, respectively. The findings on chest CT worsened in 38.4% of the patients and improved or remained stable in 61.5% of the patients. No complications occurred related to adverse events<sup>101</sup> (C).

In patients with SSc and ILD, a combination of cyclophosphamide (1 g/m<sup>2</sup>/dose per month over 12 months) with prednisone (60 mg/day over 1 month) did not produce any change in the FVC, forced expiratory volume (FEV), DLCO, or occurrence of infections after 3 years compared to cyclophosphamide alone<sup>102</sup> (A).

The FVC and DLCO did not show any difference after treatment of patients with SSc and diffuse ILD with cyclophosphamide PO (1-2.5 mg/kg/day) or IV (500-750 mg/m<sup>2</sup>) compared to untreated patients or patients treated with azathioprine over 12 months. However, the FVC and DLCO after 12 months exhibited significant improvement when the data from experimental and observational studies were analysed together. Treatment with cyclophosphamide PO or IV did not exhibit a significant difference<sup>103</sup> (A).

All of the patients with ILD and SSc using cyclophosphamide, 0.4 g/m<sup>2</sup>/month, combined with prednisone, 0.8 mg/kg/

day, exhibited improvement after 12 months (as assessed by dyspnoea scores, CT, and FVC) but relapsed after 48 months. These findings justify the use of maintenance therapy<sup>104</sup> (B).

Corticosteroids in low doses (equivalent to prednisone 5-10 mg/day) are routinely used in Brazil as maintenance treatment for patients with ILD. In cases of dc-SSc of < 5 years, special attention must be focused on the likelihood of triggering SRC (scleroderma renal crisis), which occurs in patients using prednisone  $\geq 15$  mg/day.

In a 4-week period, patients with SSc and progressive ILD (ground-glass or reticular changes at least to the venous confluence) treated with bosentan (62.5 mg twice per day for 4 weeks, and subsequently 125 mg twice per day) over 12 months did not exhibit improvement on the 6-min walk test, mortality rate, lung function test, or FVC compared to untreated patients<sup>105</sup> (A).

A retrospective study that analysed 109 patients with dc-SSc treated with mycophenolate mofetil noted a lower frequency of clinically significant lung fibrosis ( $P = 0.037$ ) and better 5-year survival ( $P = 0.027$ ) compared to 63 controls treated with other immunosuppressants<sup>106</sup> (B).

Clinical studies conducted with small numbers of patients showed that rituximab might be efficient in the treatment of ILD in patients with SSc. One study assessed 15 patients treated with rituximab (two cycles with a dose of 375 mg/m<sup>2</sup> and 2-week interval) at baseline and after 24 weeks and demonstrated a significant improvement of the FVC ( $P = 0.0018$ ) and DLCO ( $P = 0.017$ ) associated with improvement of the skin score ( $P < 0.001$ ) compared to six patients under conventional treatment<sup>41</sup> (A). Improvement of FVC and DLCO persisted after 2 years of treatment<sup>42</sup> (A).

### Recommendation 12

The ILD associated with SSc improves after treatment with cyclophosphamide. Mycophenolate mofetil and rituximab might represent alternative options for patients who are non-responsive to cyclophosphamide.

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## 13. What treatments are beneficial for pulmonary arterial hypertension in systemic sclerosis?

According to a recent meta-analysis, the prevalence of PAH is approximately 9% in patients with SSc<sup>107</sup> (B). In that population, PH might be pre-capillary (due to PAH or to ILD) or post-capillary (secondary to left-heart disease). A precise diagnosis of the mechanisms involved is required for therapeutic decision-making. A recent study noted that a reduction of the volume of alveolar diffusion of carbon monoxide (< 70%) might be a risk factor for pre-capillary PH in SSc<sup>107</sup> (B).

PH is a haemodynamic condition defined by average pulmonary artery pressure of  $\geq 25$  mmHg in rest conditions, and pulmonary capillary pressure of  $\leq 15$  mmHg measured by right-heart catheterisation.

Recommendations for the treatment of PAH were recently published by the European Society of Cardiology and the European Respiratory Society<sup>108</sup> (D). Treatment of PAH might be conventional or specific. Conventional treatment

includes general measures, such as oxygen therapy (in patients with oxygen saturation of < 90% in rest conditions or after exercise), diuretics (to correct fluid overload in right-heart failure), and digoxin (to treat right-heart failure complicated by atrial arrhythmia), in addition to anticoagulation (indicated in "severe PAH", which still lacks specific definition). Use of calcium-channel blockers, such as nifedipine, in high doses is restricted to the small group of patients (< 2%) with positive vasoreactivity (reduction of mean pulmonary artery pressure of  $\geq 10$  mmHg, thus reaching levels of  $\leq 40$  mmHg, and improvement or normalisation of the cardiac index) to the acute vasodilator challenge in haemodynamic testing<sup>108</sup> (D).

The specific treatment of PAH is based on the use of the groups of vasodilators that act on the three pathways involved in its physiopathology: prostanoids (epoprostenol, iloprost), ERAs (bosentan and ambrisentan), and phosphodiesterase type-5 inhibitors (sildenafil and tadalafil)<sup>108</sup> (D).

### Prostacyclin analogues

Epoprostenol per IV route was the first specific agent approved for the treatment of PAH. A randomised clinical study compared patients exhibiting SSc spectrum disorders treated with IV epoprostenol ( $\leq 2$  ng/kg of body weight per min) combined with conventional treatment, and conventional treatment alone, and reported the following results after 12 weeks: increase of 108 m in the distance walked in 6 min; reduction of 26 mmHg of the pulmonary artery pressure; reduction of 25.5 mm/L/min of the vascular resistance; reduction of 50% of the functional class; and improvements in the dyspnoea and fatigue scores. The mortality rates did not exhibit a significant difference. Adverse events included pain, nausea, anorexia, sepsis, cellulitis, haemorrhage, and pneumothorax<sup>109</sup> (A). However, in addition to its unavailability in Brazil, epoprostenol demands special care relative to the use of the continuous infusion pump.

Several prostacyclin analogues, such as (inhaled or IV) iloprost, treprostinil, and beraprost, also showed favourable results in patients with idiopathic PAH; however, few studies demonstrated their efficacy in SSc<sup>108</sup>(D) <sup>110</sup>(B).

### Endothelin receptor antagonists

Bosentan was assessed in randomised clinical trials, where it promoted better results in the 6-min walk test associated with haemodynamic improvement in patients with PAH, including PAH associated with SSc<sup>111,112</sup> (A). In one clinical trial, patients with severe symptoms of primary PH or secondary to SSc (functional class III-IV), distance of the 150-500 m on the 6-min walk test, mean pulmonary pressure of  $\geq 25$  mmHg, pulmonary capillary pressure of < 15 mmHg, and pulmonary vascular resistance of > 240 dyn s cm<sup>-5</sup> were randomly allocated to treatment with bosentan 62.5 mg twice per day over 4 weeks followed by 125 mg twice per day over 12 weeks, or placebo. The results of the treated group were as follows: greater distance on the 6-min walk test (difference of 76 m), improvement of the cardiac index (increase of 1.0 L min<sup>-1</sup>m<sup>-2</sup>), reduction of the pulmonary vascular resistance (reduction of 415 dyn s cm<sup>-5</sup>), and reduction in the dyspnoea index (Borg)<sup>111</sup> (A).

Ambrisentan in doses of 5-10 mg/day showed favourable results in clinical studies on patients with idiopathic PAH, as well as in initial studies including patients with SSc<sup>113,114</sup> (B).

### Phosphodiesterase type-5 inhibitors

Sildenafil was assessed in a randomised clinical trial conducted on 278 patients with idiopathic PH associated with connective tissue disorders (15% with SSc) or after surgical correction of pulmonary systemic shunt. The volunteers were given sildenafil in doses of 20 mg, 40 mg, or 80 mg three times per day over 12 weeks, which were associated with increased distance in the 6-min walk test of 45 m (+13.0%), 46 m (+13.3%), and 50 m (+14.7%), respectively. Sildenafil in all three doses induced improvement of the haemodynamic variables and the functional class. The most common adverse events were headache, face redness, hypotension, dyspepsia, and diarrhoea<sup>115</sup> (A). A *post hoc* analysis of a subgroup of patients from that same study with SSc and other connective tissue disorders showed increased distance on the 6-min walk test in the treated group. The functional class improved in 29% to 42% of the patients compared to 5% in the untreated group<sup>116</sup> (B).

Additionally, tadalafil proved to be useful in the treatment of PAH. Tadalafil was demonstrated to improve the exercise capacity, quality of life, and clinical state in a clinical study of 406 patients with PAH, of whom there were 95 volunteers with PAH that was associated with connective tissue disorders<sup>117</sup> (A).

### Combined therapy

Combined therapy is also a target of several studies and might provide an alternative option for patients who do not respond well to monotherapy<sup>108</sup> (D).

### Recommendation 13

The treatment of PAH in SSc includes conventional therapy and the following three classes of specific agents: prostacyclin analogues (epoprostenol, iloprost), endothelin receptor analogues (bosentan), and phosphodiesterase type-5 inhibitors (sildenafil, tadalafil).

## 14. What treatments are beneficial for scleroderma renal crisis?

Approximately 13% of a cohort of individuals with SSc who were followed up for 4 years exhibited SRC. Approximately 56% of the participants who eventually developed SRC were taking prednisone at study entry, compared with only 26% in the non-SRC patients (30%). In 90% of the patients, the dose of prednisone was  $\leq 10$  mg/day until the appearance of renal crisis<sup>118</sup> (B). The 5-year mortality rate of patients with SSc was 15%, and no difference was observed regarding the incidence of SRC or the mortality rate between patients using high (750-1,000 mg/day) or low (125 mg on alternate days) doses of D-penicillamine<sup>33</sup> (A).

The incidence of SRC in patients with SSc might be 2.8%. Several drug-related factors might favour the occurrence of

SRC in patients with SSc, such as the use of non-steroidal anti-inflammatory drugs (NSAIDs), steroids in high doses (> 20 mg/day), cyclosporine, penicillamine, and surgical procedures. The appearance of SRC was accompanied in the majority of the patients by severe hypertension (94%), heart failure (56%), and microangiopathic haemolytic anaemia (MAHA) (81%), with a quick progression toward kidney failure with haematuria and proteinuria. The clinical progression of SRC is severe despite aggressive antihypertensive treatment (angiotensin-converting enzyme [ACE] inhibitors, vasodilators, and beta-blockers). The mortality is high over the first days and weeks, and several patients might develop permanent kidney damage, thus requiring dialysis and kidney transplant. Treatment with ACE inhibitors over 12 months was associated with satisfactory clinical progression in 50-61% of the cases<sup>118</sup> (B).

SRC is characterised by the acute occurrence of arterial hypertension and reduced kidney function (30% reduction of the glomerular filtration) and one of the following items: MAHA, hypertensive retinopathy, pulmonary oedema, oliguria or anuria, or kidney biopsy excluding other causes. Patients with dcSSc (78% of the cases) exhibited 10% increased risk of SRC compared to lcSSc. Approximately 36% of the patients did not require dialysis; 23% were subjected to dialysis and the kidney function recovered (good prognosis); 41% were subjected to dialysis, but the kidney function did not recover (high mortality); and 33% of the survivors required dialysis over 5 years. The survival rates were 82% at 1 year, 74% at 2 years, 71% at 3 years, 59% at 5 years, and 47% at 10 years<sup>119</sup> (B).

Acute and progressive oliguria due to kidney failure and acute and progressive hypertension in patients with SSc point to the occurrence of SRC, which affects 14% of the patients 4 years after the onset of the first non-Raynaud's disease symptom. As a rule, by the time SRC sets in, 20% of the patients are already using ACE inhibitors and 60% of the patients are using corticosteroids. After a 4-year follow-up, 56% of the patients required transient or long-term dialysis, none had a kidney transplantation, and the mortality of the patients who received permanent dialysis (40%) was 90%. All of the patients were treated with ACE inhibitors, whose doses were increased after SRC set in. Several patients may require a combination with calcium-channel blockers, beta-blockers, and alpha- and beta-blockers. Survival at 1 year was 78%, whereas survival at 5 years was 69%, and 50% and 41%, respectively, when chronic dialysis was required. The prognostic factors of mortality and chronic dialysis in SRC were as follows: age > 53 years old, normal arterial pressure, and need of dialysis at the onset of SRC<sup>120</sup> (B).

The diagnostic criteria of hypertensive renal crisis in patients with SSc are as follows: systolic arterial pressure of > 140 mmHg; diastolic arterial pressure of > 90 mmHg; increases of the systolic pressure > 30 mmHg or of the diastolic pressure > 20 mmHg associated with one of the following items: increase of the serum creatinine levels of > 50% compared to baseline or serum creatinine levels of > 120% of the normal value; proteinuria > two-fold; haematuria > two-fold; thrombocytopenia with < 100,000 platelets/mm<sup>3</sup>; haemolysis; and hypertensive encephalopathy. The diagnostic criteria of normotensive renal crisis in patients with SSc are as follows: serum creatinine of > 50% compared to baseline or > 120% of the normal value associated with one of the following items:

proteinuria > two-fold; haematuria > two-fold; thrombocytopenia with < 100,000 platelets/mm<sup>3</sup>; haemolysis; and hypertensive encephalopathy.

The distribution, clinical progression, and prognosis of the infected patients were assessed based on the following diagnostic criteria of hypertensive and normotensive SRC: 87% had hypertensive SRC, 22% were using ACE inhibitors or 5% renin-angiotensin blockers or 50% corticosteroids, before SRC set in. After 1 year, 50% of the patients received dialysis or had died<sup>121</sup> (B).

With an overall incidence of 12% of SRC in patients with SSc, 20% of the patients developed SRC more than 6 months before the diagnosis of SSc, 70% developed SRC between 6 months before and after the diagnosis of SSc, and 10% developed SRC 6 months after the diagnosis of SSc. Approximately 20% of the patients exhibited satisfactory clinical progression and did not require dialysis. Of the 80% who required dialysis, only 20% could discontinue dialysis after 1 and 2 years. Kidney transplantation was indicated in 30%; all of the patients used mycophenolate mofetil, azathioprine, cyclosporine, or tacrolimus; none exhibited transplant rejection; and the kidney function recovered. The survival rate of the patients with SRC was 58% at 5 years and 40% at 10 years, and the survival rate of the patients without SRC was 90% at 5 years and 76% at 10 years<sup>122</sup> (B).

#### Recommendation 14

Patients with SSc and renal crisis should be treated with ACE inhibitors in high doses. Dialysis and kidney transplantation are restricted to the patients in whom the kidney function does not recover quickly.

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### 15. What treatments are beneficial for heart infection in systemic sclerosis?

Approximately 10-35% of the patients with SSc might exhibit heart symptoms or arrhythmias. Cardiopulmonary infection contributes to 70% of the mortality, and heart involvement contributes to 11.4-36% of the deaths<sup>123-126</sup> (C). Approximately 52-55% of the patients without clinical evidence of heart disease have alterations in the coronary flow<sup>127,128</sup> (C). A portion of the perfusion defects is fixed, and reduced heart perfusion is found in 82% of the patients<sup>129,130</sup> (C). The prevalence of coronary disease was 22% in patients with SSc, and the distribution compared to the reference population (estimated events) was 47% with typical angina, 50% with atypical angina, and 93% in patients with non-angina pain or with ventilatory restriction<sup>131</sup> (C).

Published reports have indicated the beneficial effects of vasodilators nifedipine, nicardipine, and captopril on the myocardial perfusion after treatment with dipyridamole administered intravenously<sup>132-135</sup> (C). The benefits associated with the use of nifedipine (20 mg three times per day over 1 or 2 weeks) relative to the myocardial perfusion were demonstrated using positron emission tomography and magnetic resonance imaging, which showed 38% increase of the global perfusion index and 39% reduction of the number of patients with more than one segment with perfusion defects<sup>129,136,137</sup> (C).

Patients with SSc exhibited reductions of the left ventricular ejection fraction (< 55%), right ventricular systolic depressed function, left ventricular diastolic depressed function, and 29% of the patients exhibited hypokinesia<sup>138-141</sup>(C). The beneficial action of vasodilators in myocardial dysfunction was also exemplified by the use of nicardipine (40 mg), which improved the left and right ventricular ejection fraction<sup>129,138,142</sup> (C).

The following cardiac conduction defects were found in the electrocardiographic results of patients with SSc and ventricular arrhythmias concomitantly treated with anti-arrhythmic agents (amiodarone, carvedilol, and calcium-channel blockers), cyclophosphamide, and the following vasodilators: first-degree atrioventricular block, left anterior fascicular block, and right bundle branch block, with cases > 1,000-5,000 premature ventricular contractions, nonsustained ventricular tachycardia, ventricular and supraventricular arrhythmias<sup>143</sup>(C). After 36 months of follow-up, 70% of the patients with implantable cardioverter-defibrillators exhibited normal heart rhythm and absence of shocks. The patients with ventricular tachycardia were reverted using the device<sup>144</sup> (C).

#### Recommendation 15

The frequency of heart involvement (myocardial, coronary, and arrhythmic disorders) tends to be high in patients with SSc, and specific treatment is indicated, including calcium-channel blockers (nifedipine, nicardipine), angiotensin-converting enzyme inhibitors (captopril, amiodarone, carvedilol, and myocardial revascularisation).

### Conflicts of interest

Sampaio-Barros PD: Member of the board of Abbott Laboratories, Janssen Pharmaceuticals, MSD, and Pfizer. Lectures and participation in conferences, symposia, and meetings were funded, in part, by Abbott Laboratories, Actelion Pharmaceuticals, Janssen Pharmaceuticals, MSD, Pfizer, and Roche.

Maretti GB: Received a grant to train in NFC from the Actelion Pharmaceuticals.

The other authors declare no conflicts of interest.

### Appendix Search strategies per clinical question and number of located and selected articles

#### Question 1

What are the classification criteria for systemic sclerosis?

((Scleroderma, Systemic OR Systemic Sclerosis) AND specificity[Title/Abstract]) OR ((Scleroderma, Systemic OR Systemic Sclerosis) AND (classification OR criteria) AND (sensitivity\*[Title/Abstract] OR sensitivity and specificity[MeSH Terms]ORdiagnos\*[Title/Abstract]ORdiagnosis[MeSH:noexp] OR diagnostic \* [MeSH:noexp] OR diagnosis,differential[MeSH:noexp] OR diagnosis[Subheading:noexp]))

#### Question 2

What is the role of nailfold capillaroscopy in the early diagnosis and follow-up of systemic sclerosis?

((Scleroderma, Systemic OR Systemic Sclerosis) AND specificity[Title/Abstract]) OR ((Scleroderma, Systemic OR Systemic Sclerosis) AND (classification OR criteria) AND (sensitivity\*[Title/Abstract] OR sensitivity and specificity[MeSH Terms]ORdiagnos\*[Title/Abstract]ORdiagnosis[MeSH:noexp] OR diagnostic \* [MeSH:noexp] OR diagnosis,differential[MeSH:noexp] OR diagnosis[Subheading:noexp]))

Located: 1,138

Selected: 12

#### Question 3

What is the role of the autoantibodies in the early diagnosis and follow-up of patients with systemic sclerosis?

((Scleroderma, Systemic OR Systemic Sclerosis) AND specificity[Title/Abstract]) OR ((Scleroderma, Systemic OR Systemic Sclerosis) AND (classification OR criteria) AND (sensitivity\*[Title/Abstract] OR sensitivity and specificity[MeSH Terms] OR diagnos\*[Title/Abstract] OR diagnosis[MeSH:noexp] OR diagnostic \* [MeSH:noexp] OR diagnosis,differential[MeSH:noexp] OR diagnosis[Subheading:noexp]))

Located: 1,138

Selected: 28

#### Question 4

What treatments are beneficial for skin thickening in systemic sclerosis?

(Scleroderma, Systemic OR Systemic Sclerosis) AND (cutaneous OR skin OR thick\* OR tissue) AND (randomised controlled trial[Publication Type] OR (randomised[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract]))

Located: 137

Selected: 21

#### Question 5

What treatments are beneficial for subcutaneous calcinosis in systemic sclerosis?

Scleroderma, Systemic OR Systemic Sclerosis) AND (calcinosis OR calcium OR subcutaneous)

Located: 1,374

Selected: 28

#### Question 6

What treatments are beneficial for Raynaud's phenomenon in systemic sclerosis?

(Scleroderma, Systemic OR Systemic Sclerosis) AND Raynaud AND (randomised controlled trial[Publication Type] OR (randomised[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract]))

Located: 56

Selected: 20

**Question 7**

What treatments are beneficial for ischaemic ulcers in systemic sclerosis?

(Scleroderma, Systemic OR Systemic Sclerosis) AND (ulcer OR ulcers OR ulceration OR ulcerative)

Located: 766

Selected: 8

**Question 8**

What are the maintenance treatments to prevent the recurrence of ischaemic ulcers in systemic sclerosis?

(Scleroderma, Systemic OR Systemic Sclerosis) AND (ulcer OR ulcers OR ulceration OR ulcerative) AND (recurrence OR relapse OR refractory OR follow-up OR cohort OR time factors OR response OR recrudescence OR prognosis)

Located: 270

Selected: 21

**Question 9**

What treatments are beneficial for oesophageal and intestinal hypomotility in systemic sclerosis?

(scleroderma, systemic OR systemic sclerosis) AND (esophageal diseases OR esophagus OR intestinal diseases OR intestin\* OR motility OR bloating OR distention) AND (scleroderma, systemic OR systemic sclerosis) AND (esophageal diseases OR esophagus OR intestinal diseases OR intestin\* OR motility OR dismotility OR bloating OR distention)

Located: 397

Selected: 31

**Question 10**

What treatments are beneficial for gastroesophageal reflux and its complications in systemic sclerosis?

(scleroderma, systemic OR systemic sclerosis) AND (Gastroesophageal Reflux OR Gastric Acid Reflux OR GERD OR Esophageal Reflux)

Located: 233

Selected: 12

**Question 11**

What treatments are beneficial for malabsorption syndrome in systemic sclerosis?

(scleroderma, systemic OR systemic sclerosis) AND (Malabsorption Syndromes OR absorption OR malnutrition OR nutritional status OR Intestine, Small OR Parenteral Nutrition OR Protein-Losing Enteropathies OR Exudative Enteropath\*)

Located: 508

Selected: 19

**Question 12**

What treatments are beneficial for interstitial lung disease in systemic sclerosis?

(scleroderma, systemic OR systemic sclerosis) AND (Lung Diseases, Interstitial OR Interstitial Pneumonia OR In-

terstitial Pneumonitis) AND ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random\*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading])

Located: 258

Selected: 26

**Question 13**

What treatments are beneficial for pulmonary hypertension in systemic sclerosis?

(scleroderma, systemic OR systemic sclerosis) AND Hypertension, Pulmonary AND ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random\*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading])

Located: 353

Selected: 7

**Question 14**

What treatments are beneficial for scleroderma renal crisis?

(scleroderma, systemic OR systemic sclerosis) AND (Kidney Diseases OR Acute Kidney Injury OR Renal crisis OR Hypertension, Renal OR Renal Dialysis)

Located: 1495

Selected: 7

**Question 15**

What treatments are beneficial for heart infection in systemic sclerosis?

(scleroderma, systemic OR systemic sclerosis) AND (cardiac diseases OR heart diseases) AND ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random\*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading])

Located: 267

Selected: 10

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