Articular involvement in systemic sclerosis

Jérôme Avouac, Philip J. Clements, Dinesh Khanna, Daniel E. Furst and Yannick Allanore

Abstract

Articular involvement is frequent in SSc. It contributes to disability and compromises patients' quality of life. Different aspects of articular involvement have been described, ranging from arthralgia and arthritis to joint contracture and tendon sheath involvement. Recent cohort studies examining clinical and radiographic aspects of SSc have clarified the frequency of articular involvement and identified subsets of SSc patients with a higher risk of developing joint involvement. They have also highlighted the potential contribution of inflammatory arthritis to early SSc. Some pilot studies have underlined the potential usefulness of new imaging tools, such as ultrasonography and MRI for a better evaluation of joint involvement in SSc. Current treatment strategies for SSc-related inflammatory joint disease have not been evaluated in randomized controlled trials and generally derive from RA. MTX associated with low-dose CSs is the standard care for arthritis. Other treatment strategies (LEF and i.e. biologics borrowed from RA) may bring new opportunities to treat SSc-related arthritis and even SSc per se. However, the first step will be to study and validate outcome criteria in this insufficiently studied field.

Key words: systemic sclerosis, joints, arthritis, tendon friction rubs.

Introduction

SSc is a severe CTD characterized by vascular, immune and fibrotic changes in the skin and internal organs [1]. While tethering of the skin is the clinical hallmark of SSc, many patients develop musculoskeletal symptoms during the course of their illness. Manifestations may include varying degrees of rheumatic complaints ranging from arthralgias to frank arthritis, contractures and tendon friction rubs. Articular involvement contributes to disability and impaired quality of life in SSc, reducing the ability to work or perform activities of daily living [2-6]. Indeed, several recent cross-sectional studies highlighted the major impact of articular involvement on the quality of life in SSc. Osteoarticular, muscle and soft tissue involvement may impair hand function secondary to stiff/painful joints, reduced dexterity and/or grip [7, 8]. Our objective is to provide an overview of the spectrum of articular involvement in SSc. We will further underscore the multi-system nature of this condition and will review the different therapeutic approaches to musculoskeletal involvement, with a special focus on biologics that should soon be evaluated in this context.

Clinical presentations

Joint involvement eventually affects 46-97% of patients with SSc [2, 9]. The systematic cross-sectional examination of the EULAR Scleroderma Trials and Research (EUSTAR) registry identified clinical synovitis, defined by tender and swollen joints, and tendon friction rubs, defined by a leathery, rubbing, squeaking sensation detected as the tendon is moved actively or passively, in 16% (1191/7286) and 11% (802/7286) of SSc patients, respectively (Table 1) [10]. Joint involvement may be an initial manifestation that precedes the onset of RP or may arise concomitantly and therefore might be considered an early indicator of SSc [2, 9]. The frequency of joint involvement as an initial sign of SSc has not been defined accurately and range from 12% to 65% of SSc patients. Thus it is important in patients presenting only with articular involvement (arthralgia, synovitis and/or tenosynovitis) to search for early signs of SSc, such as RP and puffy fingers. In case of early SSc suspicion, simple examinations such as capillaroscopy and SSc-specific antibodies detection should be performed. However, inflammatory arthritis and

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RHEUMATOLOGY

Review

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Articular involvement is frequent in SSc. It contributes to disability and compromises patients' quality of life. Different aspects of articular involvement have been described, ranging from arthralgia and arthritis to joint contracture and tendon sheath involvement. Recent cohort studies examining clinical and radiographic aspects of SSc have clarified the frequency of articular involvement and identified subsets of SSc patients with a higher risk of developing joint involvement. They have also highlighted the potential contribution of inflammatory arthritis to early SSc. Some pilot studies have underlined the potential usefulness of new imaging tools, such as ultrasonography and MRI for a better evaluation of joint involvement in SSc. Current treatment strategies for SSc-related inflammatory joint disease have not been evaluated in randomized controlled trials and generally derive from RA. MTX associated with low-dose CSs is the standard care for arthritis. Other treatment strategies (LEF and i.e. biologics borrowed from RA) may bring new opportunities to treat SSc-related arthritis and even SSc per se. However, the first step will be to study and validate outcome criteria in this insufficiently studied field.

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Introduction

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Clinical presentations

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Tendon involvement

Tendon abnormalities are described as leathery crepitus on palpation of the knees, wrists, fingers, and ankles, related to fibrinous deposits on the surface of tendon sheaths and overlying fascia [19]. In the leg, tendon rubs are usually localized to the tendons of the tibialis anterior and the Achilles tendon, or less frequently, the peroneous muscles. In the forearm the source of this rub is usually the tendons of the flexor or extensor muscles immediately proximal to the wrist. Median nerve compression with CTS may occur, presumably from changes in the tendon sheaths beneath the transverse carpal ligament. Since CTS is often the symptom that brings the patient to a physician, all physicians should be aware of its association with SSc. In particular, the co-occurrence of Raynaud’s syndrome and puffy fingers together with CTS must make the physician investigate his patients in depth for potential connective tissue disorder.

Joint involvement

Generalized arthralgias with slight pain and stiffness are the usual presentations of articular involvement; however, true joint inflammation may occur and be a source of initial diagnostic confusion [12–17]. The onset may be acute or insidious, and oligoarticular or polyarticular in pattern. Virtually all joints may be affected, although the fingers (in particular the MCP and PIP joints), wrists and ankles predominate. The course of the joint manifestations tends to be intermittent or chronic remittent. As the disease progresses, there is tethering and contracture of the underlying joints with impairment of movement and function. Joint contracture, defined as an abnormal, often permanent shortening, as of muscle or scar tissue, which results in distortion or deformity, especially of a joint of the body, was observed in 31% (2264/7286) of patients in the EUSTAR registry. Clinical findings are often minimal at the onset aside from features that may betray the presence of early SSc. Some patients exhibit localized joint tenderness or swelling, while joint effusions are less frequent and they are usually mild [18].

Laboratory findings

RF positivity occurs in up to 30% of SSc patients [21, 22]. This test seems non-specific and does not distinguish SSc patients with musculoskeletal manifestations from those not so affected [22]. RF may also be seen in patients with SSc-associated secondary SS, which is not uncommon in SSc, with a prevalence of 12% in a large population of 1132 SSc patients, and occurs more frequently in patients with the limited cutaneous subset and positive ACAAs [23–25]. The search for anti-CCP antibodies might be of great help in the identification of the infrequent cases of true SSc-RA overlap [26]. Different cross-sectional studies estimate the point prevalence of anti-CCP antibodies in patients with SSc as from 1 to 15%. These studies also suggest the potential diagnostic value of this test to identify patients with SSc also having RA, with a sensitivity ranging from 50 to 100% and a specificity of ~95% [26–32] (Table 2). However, the presence of RF or anti-CCP antibodies does not seem to correlate with the clinical or radiographic pattern of arthritis, although...
the studies so far have been limited by small sample sizes [17, 22]. Analysis of the SF generally reveals normal or modestly increased leucocyte concentrations of <2000 cells/mm³ and a predominantly mononuclear infiltrate [33]. Synovial biopsies from SSc joints have shown histological evidence of inflammation, with lymphocytic and plasma cell infiltration and superficial fibrin deposits, but rarely if ever pannus.

Articular involvement as a correlate of prognosis and diagnosis of SSc

Joint involvement

Few studies have looked at the subsets of SSc patients with a higher risk of developing arthritis. In the EUSTAR registry, patients with synovitis and early disease (date of first non-Raynaud symptom <3 years) were more likely to experience diffuse cutaneous thickening (57 vs 33%, P < 0.0001). This observation raises the question of the prognostic value of synovitis in patients with early SSc to identify those with a potential risk for developing dcSSc. The likelihood of severe vascular (pulmonary hypertension) and muscular (muscle weakness) involvement was higher in patients with synovitis, regardless of their cutaneous subset or their disease duration. The proposition that synovitis might be a predictive factor of the diffuse cutaneous subset, carrying a poor prognosis, is now under investigation in the prospective follow-up of SSc patients included in the EUSTAR database.

One study also identified an association between synovitis and elevated acute phase reactants (ESR ≥ 28 mm/h and CRP ≥ 10 mg/l), suggesting that joint involvement might be associated with systemic inflammation in SSc [10, 22]. This is partly supported by the infiltration of inflammatory cells in SSc synovial biopsies [33].

Tendon involvement

Tendon involvement is more prevalent in patients with the diffuse cutaneous subset and early disease [10, 34]. It is also associated with signs of severe vascular, muscular, and renal involvement and decreased survival. In particular, recent data have highlighted the independent association, in multivariate analysis, between tendon friction rubs and digital ulcerations, muscle weakness, pulmonary fibrosis on plain chest X-ray and proteinuria detected with a urinalysis dipstick. There has also been recent documentation that tendon friction rubs are associated with active disease [35].

These results highlight that tendon friction rubs are an important physical finding because they often precede widespread skin thickening and can be considered as a sign predictive of poor outcome. Thus searching for friction rubs should be a routine part of the physical examination, since they are of predictive value regarding classification, severity and progression.

Radiological features: structural osteoarticular lesions

Many distinctive radiographic abnormalities have been recognized in patients with SSc. Articular lesions, from juxta-articular osteoporosis and joint space narrowing to frank erosions, have been reported throughout the MCP, PIP and DIP joints, as well as the wrist. Patterns of SSc arthropathy range from that resembling erosive OA or PsA with relative sparing of MCP joints to changes reminiscent of RA (Fig. 1). A seemingly distinctive erosion or focal resorptive change, localized to the dorsal aspect of the MCP and PIP heads, has been reported. Their aetiology may be related to capsular or ligamentous traction rather than true synovial inflammation [21]. In addition, selective involvement of the first CMC phalangeal joint might be a distinctive feature of SSc. The detection of pencil-in-cup deformity in hands and feet, also observed in PsA and other rheumatic diseases, has been reported [36]. These articular features may be associated with non-articular abnormalities, in particular skin atrophy, s.c. calcinosis and digital tuft resorption, which are among the most distinctive radiographic findings in SSc (Fig. 1) [17, 22].

The frequency of hand radiographic erosions is between 5 and 40% (Table 3) [2, 17, 21, 22, 29, 37-40]. Joint space narrowing is not uncommon in SSc; its point prevalence on X-ray being ~30%, with a predominant involvement of DIP joints (Table 3) [2, 17, 21, 22, 40]. Joint space narrowing has been noted with ultrasonography in 8/45 (18%) SSc patients.

SSc patients with erosions on X-ray may have erosions typical of RA in the hands, with MCP and PIP distribution and with juxta-articular osteoporosis plus joint space narrowing. However, a more distal distribution can also occur, which could be related to SSc or digital OA, since the majority of SSc patients are post-menopausal women. However, a recent cross-sectional study

<table>
<thead>
<tr>
<th>TABLE 2 Point prevalence of anti-CCP antibodies in SSc</th>
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<tr>
<td>Avouac et al. [26] (n = 120)</td>
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<tr>
<td>-------------------------------</td>
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<tr>
<td>Prevalence of anti-CCP, n (%)</td>
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<tr>
<td>Sensitivity of anti-CCP for the diagnosis of associated RA, %</td>
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Downloaded from https://academic.oup.com/rheumatology/article-abstract/51/8/1347/1841964 by guest on 22 April 2019
observed the presence of DIP joint erosions and DIP joint space narrowing in 15 and 21% of SSc patients, respectively, vs 0 and 5% in a group of healthy controls matched for age and sex, respectively, suggesting that DIP changes might be specific of SSc [22]. DIP involvement in SSc will require confirmation through further work and larger studies.

In a recent prospective cohort study involving 120 patients, erosive arthritis, defined as the occurrence of both erosions and joint space narrowing, was found in 22 (18%) SSc patients [22]. The 5-year longitudinal follow-up of these patients, with a systematic examination of dual time-point X-rays, showed a total radiographic progression of erosive arthritis in 24 (23%) SSc patients. Among these, 10 had developed incident erosive arthritis, defined by the occurrence on the second X-ray of at least one erosion and joint space narrowing, and 14 experienced worsening of their baseline lesions, defined by the occurrence on the second X-ray of at least one new erosion and/or joint space narrowing [41]. The presence of erosive arthritis was not associated at baseline with any SSc characteristics or with the presence of RF or anti-CCP2 antibodies. This is in accordance with previous studies that failed to show a correlation between erosive arthritis and clinical or laboratory variables [2, 21].

Despite the high frequency of erosive arthritis in this cohort, no independent predictor of the progression of erosive arthritis in SSc was identified [41]. This lack of any predictive factor for erosive arthritis might be related to the multifactorial aspects of SSc arthropathy. An overlap with RA should be considered, but was found in only 3 of 103 patients; two had erosive arthritis at baseline while the third patient had worsened erosive arthritis. The possibility of erosive OA should also be considered, especially since persistent clinical synovitis (defined by tender and swollen joints) occurred in only 5/24 (21%) of the patients with progression of erosive arthritis. Furthermore, in this latter study there was a high frequency of DIP joint involvement [11/24 (46%)] and a large proportion of the patients were post-menopausal women (83%). On the other hand, radiographic progression of erosive arthritis also occurred in the wrist [11/24 patients (46%)], MCP [7/24 (29%)] and

![Hand and foot radiographic lesions in SSc. (A) Erosive radiographic arthritis characterized by erosions and joint space narrowing involving the PIP and DIP joints (white arrows). (B) Typical SSc radiographic features associating erosive arthritis of PIP and DIP joints (white arrows), s.c. calcinosis (hash) and acro-osteolysis (asterisk). (C) SSc-related arthropathy involving the second and third PIP joints, resembling PsA (white arrows). (D) Foot erosive radiographic arthritis involving MTP joints (white arrow) associated with acro-osteolysis (asterisk).](https://academic.oup.com/rheumatology/article-abstract/51/8/1347/1841964)
PIP [9/24 (38%)], which suggests that these erosive changes were not related only to coincident OA.

In our view, some patterns of erosive arthropathy can be directly related to SSc and considered as an integral feature of this disease; however, DIP involvement suggests coincident OA.

New imaging techniques for the evaluation of osteoarticular involvement in SSc

The recent development of power Doppler ultrasonography, which allows the assessment of synovial vascularity (and thus active inflammation), and MRI as diagnostic tools and outcome criteria in RA has led to a substantial improvement in disease evaluation. Preliminary and promising data are now available in SSc from these non-invasive techniques that do not use ionizing radiation [42].

### Table 3: Prevalence of structural lesions in SSc

<table>
<thead>
<tr>
<th></th>
<th>Frequency of joint space narrowing, $n$ (%)</th>
<th>Frequency of erosions, $n$ (%)</th>
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<tbody>
<tr>
<td>X-ray evaluation</td>
<td></td>
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<tr>
<td>Avouac et al. [22]</td>
<td>35 (28)</td>
<td>25 (21)</td>
</tr>
<tr>
<td></td>
<td>Wrist: 13 (37)</td>
<td>Wrist: 17 (68)</td>
</tr>
<tr>
<td></td>
<td>MCP: 12 (34)</td>
<td>MCP: 9 (36)</td>
</tr>
<tr>
<td></td>
<td>PIP: 14 (40)</td>
<td>PIP: 10 (40)</td>
</tr>
<tr>
<td></td>
<td>DIP: 25 (71)</td>
<td>DIP: 18 (72)</td>
</tr>
<tr>
<td></td>
<td>13 (34)</td>
<td>15 (40)</td>
</tr>
<tr>
<td></td>
<td>Wrist: 2 (15)</td>
<td>Wrist: 4 (31)</td>
</tr>
<tr>
<td></td>
<td>MCP: 2 (15)</td>
<td>MCP: 9 (60)</td>
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<tr>
<td></td>
<td>PIP: 4 (31)</td>
<td>PIP: 3 (20)</td>
</tr>
<tr>
<td></td>
<td>DIP: 12 (92)</td>
<td>DIP: 7 (47)</td>
</tr>
<tr>
<td>Baron et al. [2]</td>
<td>10 (24)</td>
<td>ND</td>
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<tr>
<td></td>
<td>102 (61)</td>
<td>30 (18)</td>
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<tr>
<td></td>
<td>ND</td>
<td>12 (22)</td>
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<tr>
<td></td>
<td>ND</td>
<td>11/75 (16)</td>
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<tr>
<td></td>
<td>29 (71)</td>
<td>8 (19)</td>
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<tr>
<td></td>
<td>PIP: 9 (31)</td>
<td>MCP: 4 (50)</td>
</tr>
<tr>
<td></td>
<td>DIP: 16 (55)</td>
<td>PIP: 4 (50)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DIP: 3 (38)</td>
</tr>
<tr>
<td>La Montagna et al. [17] (n = 76)</td>
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<tr>
<td></td>
<td>Wrist: 13 (17)</td>
<td>8 (10.5)</td>
</tr>
<tr>
<td></td>
<td>PIP: 31 (41)</td>
<td>ND</td>
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<tr>
<td></td>
<td>DIP: 41 (54)</td>
<td></td>
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<tr>
<td>Brun et al. [38]</td>
<td>10 (24)</td>
<td>ND</td>
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<tr>
<td></td>
<td>102 (61)</td>
<td>30 (18)</td>
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<tr>
<td>Koutaisoff et al. [40] (n = 167)</td>
<td>ND</td>
<td>12 (22)</td>
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<tr>
<td>Basset et al. [37]</td>
<td>ND</td>
<td>11/75 (16)</td>
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<td></td>
<td>29 (71)</td>
<td>8 (19)</td>
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<tr>
<td>Ingegnoli et al. [29] (n = 75)</td>
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<tr>
<td>Erre et al. [39]</td>
<td>8 (18)</td>
<td>5 (11)</td>
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<tr>
<td></td>
<td>MCP: 8 (100)</td>
<td>Wrist: 1 (20)</td>
</tr>
<tr>
<td></td>
<td>PIP: 2 (25)</td>
<td>MCP: 4 (80)</td>
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<tr>
<td>Ultrasounds</td>
<td></td>
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<tr>
<td>Cuomo et al. [43]</td>
<td>8 (18)</td>
<td>5 (11)</td>
</tr>
<tr>
<td></td>
<td>MCP: 8 (100)</td>
<td>Wrist: 1 (20)</td>
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<tr>
<td></td>
<td>PIP: 2 (25)</td>
<td>MCP: 4 (80)</td>
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<tr>
<td>MRI</td>
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<tr>
<td>Low et al. [44]</td>
<td>ND</td>
<td>7 (41)</td>
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<td></td>
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<td>Wrist: 2 (29)</td>
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<td>MCP: 5 (71)</td>
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<td></td>
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<td>PIP: 2 (23)</td>
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</table>

ND: no data.

Articular involvement

An Italian study included 45 consecutive patients with SSc-assessed osteoarticular involvement using ultrasonography [43]. Joint effusion and synovial proliferation were found in 22 (49%) and 19 (42%) of the SSc patients, respectively (Table 1). Synovial proliferation was associated with increased IA power Doppler in 11 of them. The prevalence of synovitis detected with US (i.e. effusion and/or synovial proliferation) was significantly higher than that found by clinical examination (i.e. tenderness and/or swelling) (26 vs 15 out of 45 cases, $P = 0.03$). Some correlate between synovitis and acute phase reactants was also observed [41].

MRI is also a very promising tool to detect synovitis (Fig. 2A). Inflammatory joint disease of the hand has been assessed by MRI in 17 patients with a history of joint pain or swelling [44]. Ten patients had inflammatory MRI findings with synovitis ($n = 8$), joint effusion ($n = 7$) or tenosynovitis ($n = 8$) (Table 1). In another series of 17 SSc patients with arthralgias but no overt inflammatory
arthritis, MRI showed synovial inflammation in 47% of the 17 SSC patients studied, while USs showed synovial inflammation in 100% of the 8 SSC patients studied [45].

With regards to vasculopathy in SSC, magnetic resonance angiography (MRA) is an appealing technique to assess hand vascular involvement. MRA also allows detection of synovitis; in one study evaluating hand MRA in 38 SSC patients, 19 patients had one or more joints with synovitis and 4 patients had tenosynovitis at one or more sites (Table 1 and Fig. 2B) [46]. The relative sensitivity of MRI compared with MRA for synovitis detection has not been examined.

These modern techniques have also been used to describe structural articular lesions. Point prevalence of erosions assessed by ultrasonography on 45 SSC patients was 11% (5/45 patients) (Table 3) [43]. In the two studies using MRI, hand erosions were detected in 16% (6/38 patients) and 41% (7/17 patients) (Table 3) [44, 46].

Tendon involvement

The prevalence of tendon involvement has been assessed by MRI in a preliminary study performed on 17 patients; eight had tenosynovitis, either of flexor \( n = 7 \) or extensor \( n = 3 \) tendons (Table 1) [44]. The frequency of tendon involvement has not yet been assessed by US. However, US and MRI might be useful to discriminate tenosynovitis secondary to fibrous deposits on the surface of the tendon sheaths from the changes of inflammatory tenosynovitis (Fig. 2C).

The results of these studies support the need to validate these very promising imaging techniques in SSC, perhaps using the OMERACT filter [47]. The OMERACT process involves consensus on outcome measures and is based on the OMERACT filter, composed of three key components (truth, discrimination and feasibility). Thus larger sample sizes and additional cross-sectional and prospective approaches are warranted to better define the proper technique of study and to perform the studies needed to validate the measures for clinical trials. In addition, US and MRI/MRA are techniques that could be developed to allow assessment of osteoarticular involvement and SSC-related vasculopathy simultaneously that would be of great value for this specific disease and provide objective measures of involvement and responses to treatment.

**Treatment**

**Joint involvement**

**Outcome measurements**

Symptomatic therapies or DMARDs have not yet been evaluated for the treatment of articular involvement in SSC by randomized controlled trials. At present, there are no agreed-upon outcome variables that have been validated for the musculoskeletal system, with the exception of the HAQ-disability index (HAQ-DI) [48]. Thus the SSC research community needs to study and validate several outcomes, using the OMERACT filter, which could include combined response criteria similar to the ACR Response Criteria or DAS-28, DAS-44 or DAS-55 and its components. Some indirect measures such as the scleroderma HAQ-DI (including its visual analogue scale global and pain components) and short-form-36 health survey (SF-36) have already been validated [15, 49–52]. Others need at least some corroborative as measures of articular and periarticular disease, such as the ESR, CRP and physician global measures.

**Treatment**

The management of articular involvement is essentially supportive and symptomatic. For the most part, arthralgias will respond to simple NSAID treatment. Caution should be exercised, however, with this class of drugs because of the enhanced risk of gastro-oesophageal abnormalities or bleeding and impaired renal function in this group of patients. Low-dose CSs (<10 mg/day) may

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**Fig. 2** Detection of inflammatory joint and tendon involvement with MRI. (A) MRI showing radiocarpal and mediocarpal joint synovitis (white arrows). (B) MRA revealing a synovitis of the second PIP joint (white arrow). (C) Inflammatory tenosynovitis around the third finger (white arrow).
also be used for the symptomatic treatment of inflammatory arthritis or tenosynovitis, although the risk of renal crisis should be carefully considered (especially in diffuse SSC patient within the first 5 years of SSC onset and probably also taking into account of the presence or not of RNA polymerase III antibodies) whenever these drugs are used. By analogy with RA, MTX may be used for the treatment of inflammatory arthritis. The s.c. or i.m. routes of administering MTX may improve absorption in SSC patients, many of whom have covert malabsorption [53].

Other immunosuppressive drugs may be used, such as AZA or CYC. However, secondary analyses of the scleroderma lung study (which evaluated eight joints only) did not show any significant effects on articular outcomes of CYC. In particular, there was no significant difference between placebo and CYC groups for joint swelling and joint tenderness in the eight joint counts at 12 and 24 months [54].

A pilot study performed on seven women with SSC and severe and refractory inflammatory joint involvement suggested the efficacy of 6 months of IVIG therapy to reduce joint pain/tenderness (assessed by visual analogue scales), and improve of quality of life (assessed by the Dreiser Algo-Functional Index and the HAQ). However, the costs of immunoglobulins might limit their use to patients with very severe and refractory articular involvement who have failed other DMARDs [55].

Biologics have been the starting point of a new era in the treatment of inflammatory rheumatic conditions, and it is regrettable that no randomized controlled trial has been performed yet in SSC. The efficacy of TNF-α inhibitors on inflammatory joint symptoms has been suggested in a retrospective study performed on 18 patients treated with etanercept during a 2–66 month period [56]. Fifteen of these 18 patients had positive responses (not defined in the report that has the limited format of a letter to the editor), with a significant decrease in signs of inflammation or synovitis on follow-up examination and complete resolution of joint symptoms in some patients. Mean HAQ-DI scores also decreased with therapy, paralleling the improvement in joint disease. Despite these promising preliminary results, no other study has assessed the potential efficacy of TNF-α inhibitors in SSC-related arthritis. This could be explained by the issue of the safety of this therapeutic class in SSC. First, one case of fatal exacerbation of fibrosing alveolitis has been reported in an SSC patient following adalimumab treatment [57]. Very rarely, other cases of fatal exacerbation of pulmonary fibrosis while on treatment with TNF-α inhibitors have also been described in RA [58].

In addition, in a 26-week open-label pilot study performed on 16 patients and aiming to assess the safety of infliximab in dcSSC, 127 adverse events (10 severe) occurred in 16 patients. Of these, 19 adverse events were directly related to infliximab treatment. Moreover, infusion reactions directly related to infliximab led to early treatment discontinuation in 8/16 patients [59]. Separately, infliximab did not show clear overall benefit at Week 26, although articular involvement was not considered/taken as an outcome measure. Thus these data may limit the further use of these drugs in SSC-related arthritis except for use in a research-based clinical trial or a formal randomized clinical trial.

A three-round Delphi exercise was recently performed among EUSTAR centres to obtain expert consensus on the use of TNF-α inhibitors in SSC [60]. Most EUSTAR experts recommended the use of TNF-α antagonists only in randomized controlled clinical trials and discouraged the off-label use in individual patients outside of clinical trials. Arthritis was considered as a manifestation that might respond to TNF-α antagonists, and the group recommends that the response of SSC arthritis to TNF-α antagonists should be investigated in more detail. In contrast, other manifestations of SSC such as fibrosis were not anticipated to benefit from treatment with TNF-α antagonists. Thus it seems reasonable to await consistent, controlled trials regarding the efficacy for joint symptoms and safety of TNF-α inhibitors in SSC.

Rituximab, a chimeric mAb against the protein CD20 that demonstrated efficacy in RA, might also represent hope in the treatment of SSC arthritis. However, no study has assessed this drug in this specific indication yet. Open-label trials seem promising regarding the potential efficacy of rituximab for treatment of the skin and pulmonary manifestations of SSC, although articular involvement was not evaluated in any of these studies [61–63]. Further studies assessing the efficacy of rituximab in SSC-related joint disease are now warranted before recommending this treatment. The outcome of a few patients with SSC-related polyarthritis treated with tocilizumab or abatacept has been recently reported as an abstract from the EUSTAR database [64]. Tocilizumab or abatacept appeared to be safe and to improve joint involvement after 3–6 months in refractory SSC-arthritis patients. Larger controlled, randomized studies with longer follow-up are now warranted to determine rigorously the safety and efficacy of these drugs in SSC. However, these preliminary reports suggest that biologics may open major perspectives in SSC-related arthritis. While potentially improving arthritis and quality of life, the effects on fibrosis should also be monitored.

The current literature on rehabilitation techniques in SSC consists of studies evaluating the effectiveness of paraffin wax treatment, hand and face stretching exercises, connective tissue massage and joint manipulation, splints, aerobic exercise and resistance training. The data seem promising, except for splints, for improvement in joint motion, hand function and cardiopulmonary endurance [65]. However, the majority of studies involved small sample sizes and no control groups [66]. Thus larger randomized controlled studies are needed to fully determine the effectiveness of rehabilitation techniques for persons with SSC.

Surgery of the hand for SSC is used but the goals of surgery are limited. They include pain relief, repositioning the digits, providing a functional position of fusion and, in some cases, modest mobilization through resection.
arthroplasty to marginally improve finger function for patients with marked pre-existing limitations [67]. Surgical reconstruction of severely flexed PIP joints by straightening and fusing them is often successful if the MCP joints are mobile. This procedure may increase function and reduce the frequency of dorsal skin ulceration. Some rigid, deformed digits benefit from MCP joint resection to overcome contraction, reposition the digits and introduce a small range of mobility. If surgery is contemplated then local or regional anaesthesia is preferred for patients, particularly in patients who have ongoing cardiac or pulmonary manifestations of SSc. Moreover, severe narrowing of the oral aperture can result in difficulty with orotracheal intubation, and paediatric tubes for intubation can be considered. In the hands of a hand surgeon with experience in the surgical management of SSc hand surgery, surgical wounds generally heal well enough following resection of the heads of the approximating joints before fusing the PIP or DIP joints [68].

Tendon involvement

The treatment of tendon involvement is usually symptomatic and supportive. For the most part, tenosynovitis will respond to NSAIDs or low-dose of CSs, although the toxicity of these approaches require appropriate follow-up. Surgery may be required in the very rare cases of tendon rupture. In case of CTS, CSs can be injected under the retinaculum. The injection usually brings rapid relief of the symptoms. Surgical carpal tunnel release is usually very effective in symptomatic and refractory patients.

Conclusion and perspectives

Skeletal involvement is frequent in SSc and represents a heavy burden. It is multifaceted and injury of several structures can occur leading to major disability. Recent clinical and radiographic studies have allowed a better estimation of the frequency of joint involvement and identified subsets of SSc patients with the higher risk of developing joint involvement. Several pilot studies have underlined the potential usefulness of new imaging techniques such as ultrasonography, MRI or MRA. Larger studies are now needed to confirm these promising results and validate these tools for clinical trials and routine practice. Finally, although the understanding of osteoarticular pathogenesis has significantly increased in the last few years, optimal treatments of inflammatory joint disease remain to be determined and appear as a major challenge for improving SSc morbidity and patients’ quality of life. To that end, the study and validation of outcome measures in this field must be put urgently on the research agenda of the SSc community. Thereafter, one may have the chance to perform rigorous randomized controlled trials assessing the potential input of the many relevant available and upcoming drugs and therefore offering some hope in a disease that remains devastating.

Rheumatology key messages

- Articular involvement could be a component of early SSc spectrum.
- Articular involvement is a marker of active SSc disease.
- Ultrasonography and MRI are interesting tools to detect synovitis/tenosynovitis in SSc.

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