How I treat patients with systemic sclerosis in clinical practice

HOW I TREAT PATIENTS WITH SYSTEMIC SCLEROSIS IN CLINICAL PRACTICE.

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Abstract

Systemic sclerosis (SSc) or scleroderma is a disorder of the connective tissue affecting the skin, and it is often associated with visceral involvement. The predominant pathological features of SSc are autoimmunity, vasculopathy, and fibrosis. Progressive fibrosis is associated with changes in the microcirculation of the involved organs. Here, we review the clinical features of systemic sclerosis and describe the best practice approaches for its management, reviewing available guidelines and recommendations and providing experts' insights.

Introduction

Systemic sclerosis (SSC) or scleroderma is an autoimmune disorder of the connective tissue affecting the skin that is often associated with visceral involvement. It is characterized by excessive collagen deposition in the skin and internal organs, resulting in progressive tissue fibrosis and with changes in the microcirculation leading to secondary Raynaud's phenomenon and obliterative vasculopathy.

Overall, the estimated prevalence is 25 cases/100,000, the incidenceis 0.06-1.9 years/100,000, and it is prevalent in females (mean 4:1). In detail, prevalence ranges from 0.7/100,000 to 53/100,000 depending on demographics and the country of residence, with higher numbers in the USA as compared to Europe or Japan. Age at onset is between 35 and 65 years (1,2).

Pathogenesis is multifactorial and includes genetic factors such asHLA (HLA A1, B8, DR1, DR3, DR5, DR11), and environmental factors such as viruses (Cytomegalovirus, parvovirus B19), ortoxic substances (silica, silicone prostheses, polyvinyl, benzene, organic solvents, certain drugs, adulterated rapeseed oil)(1,2).

SSc has a highly variable evolution, ranging from the acral-localized form to rapid swelling lesions that spread quickly to all areas of the skin including the trunk, and to the visceral involvement (3).

SSc frequently affects internal organs such as the lungs, heart and the gastrointestinal tract (GI), all of which significantly contribute to morbidity and reduced quality of life in these patients. Overall, the prognosis of scleroderma is influenced by visceral involvement (especially of the lung), as well as cardiac and renal involvement.

Even if survival has improved considerably in the last thirty years, SSc has one of the highest mortality rates among the rheumatic diseases. Cumulative survival following diagnosis has been estimated 74.9% at 5 years and 62.5% at 10 years. The common causes of death are pulmonary fibrosis and pulmonary arterial hypertension (PAH) (4).

Overview of Current Guidelines and Recommendations

SSc therapy is still difficult to manage and yet is not well defined. It must consider the various pathways involved in the disease: activation of T lymphocytes, vascular disease due to vasospasm and endothelial immune damage, and abnormal stimulation of fibroblasts resulting in excessive deposition of extracellular matrix. Therefore, SSc therapy includes steroid and immunosuppressants, vasoactive drugs (vasodilators and endothelial protectors), and anti-fibrotic agents. (5,6)

The EULAR has published in 2016 updated evidence-based, consensus-derived recommendations for the treatment of SSc (7).

As compared to the previous (2009) EULAR recommendations for the treatment of SSc, the updated recommendations include several new therapies for specific SSc-related organ involvement. The greatest changes have been made inthe treatment of vascular complications. These changes include the introduction of phosphodiesterase type 5 (PDE5) inhibitors for SSc-related RP and digital ulcers (DUs), riociguat and new aspects of endothelin receptor antagonists (ERAs), prostacyclin analogues and PDE5 inhibitors for SSc-related PAH. New recommendations regarding the use of fluoxetine for SSc-related RP were also added.

The task force consisted of 32 SSc clinical experts from Europe and the USA. All the EULAR Scleroderma Trials centers and research groups were invited to submit and select clinical questions concerning SSc treatment using a Delphi approach. Accordingly, 46 clinical questions addressing 26 different interventions were selected fora systematic literature review. The new recommendations were based on the available evidence andwere developed during a consensus meeting with clinical experts and patients. The procedure resulted in 16 recommendations being developed (instead of 14 in 2009) that address the treatment of several SSc-related organ complications: Raynaud's phenomenon, digital ulcers, pulmonary arterial hypertension, skin and lung disease, scleroderma renal crisis and gastrointestinal involvement.

In Raynaud's phenomenon, a meta-analysis of randomized control trials (RCTs) on dihydropyridine-type calcium antagonists indicates that nifedipine (9-16) and PDE5 inhibitors (Sildenafil, Tadalafil, Vardenafil) (16-22) reduce the frequency and severity of SSc-RP attacks. Oral nifedipine with PDE5 should be considered as first-line therapy for SSc-RP. A meta-analysis of RCTs on prostanoids indicates that intravenous iloprost reduces the frequency and severity of SSc-RP attacks. Intravenous iloprost should be used for the treatment of SSc-RP attacks after oral therapy. Fluoxetine may also improve SSc-RP attacks (23).

In digital ulcers in patients with SSc: Two RCTs indicate that intravenous iloprost is effective in healing digital ulcers in patients with SSc (24-25). A meta-analysis of RCTs and results of an independent RCT suggest that PDE5 inhibitors improve healing of digital ulcers in patients with SSc.

In 2013, two meta-analyses compared i.v. iloprost, iloprost for oral use, trepronistil and beraprost. Authors reported that small sample sizes, few comparative trials, and heterogeneity limited the conclusions. However, the results suggested a role for PDE-5 inhibitors in the healing of digital ulcers; bosentan and i.v. iloprost may prevent their recurrences (26-28). Moreover, the results of a small RCT indicate that PDE5 inhibitors may prevent the development of new digital ulcers in SSc.

Lately, the efficacy of bosentan in reducing the number of new digital ulcers has been confirmed in two high-quality RCTs. Bosentan should be considered for reducing the number of new digital ulcers in SSc, especially in patients with multiple digital ulcers despite the use of calcium channel blockers, PDE5 inhibitors or iloprost therapy (29-30).

In SSc-PAH: Several ERAs (ambrisentan, bosentan and macitentan) (31-33), PDE5 inhibitors (sildenafil, tadalafil) and riociguat have been approved for the treatment of PAH associated with connective tissue diseases (CTDs). One high-quality RCT on patients with SSc indicates that continuous intravenous epoprostenol improves exercise capacity, functional class and hemodynamic measures in SSc-PAH. Intravenous epoprostenol (2 ng/Kg/min) should be considered for the treatment of patients with severe SSc-PAH (class III and IV) since improvement has been seen in the Walk Test, in NYHA, in the Borg dyspnea index, in pulmonary artery pressure (PAP), in right atrial pressure, and in Cardiac index (34).

Other prostacyclin analogues (iloprost, treprostinil) have also been registered forthe treatment of PAH associated with CTDs. Sitaxentan use has been discontinued due to hepatotoxicity.

In Skin and lung disease: Two RCTs and their re-analysis have shown that methotrexate improves skin score in early diffuse SSc. Positive effects on other organ manifestations have not been established (35-38).

Cyclophosphamide should be considered for the treatment of SSc-related interstitial lung disease (ILD) (39-44).

Regarding hematopoietic stem cell transplantation (HSCT), two RCTs have shown improvement of skin involvement and stabilization of lung function in patients with SSc, while a third, large RCT reports improvement in event-free survival in patients with SSc as compared to cyclophosphamide-treated subjects. HSCT should be considered for the treatment of selected patients with rapidly progressive SSc at risk of organ failure. Given the high risk of treatment-related side effects and early treatment-related mortality, careful selection of patients with SSc for this kind of treatment and the experience of the medical team are of fundamental importance (45-46).

In scleroderma renal crisis (SRC): many studies have shown benefits in survival with the use of ACE inhibitors in patients with SRC. Experts recommend the immediate use of ACE inhibitors in the treatment of SRC (47-51). Glucocorticoids are associated with a higher risk of SRC; therefore blood pressure and renal function should be carefully monitored in these patients (52).

In SSc-related gastrointestinal disease: the experts recommend using proton pump inhibitors (PPIs) for the treatment of SSc-related gastroesophageal reflux disease (GERD) and the prevention of esophageal ulcers and strictures (53-57). Prokinetic

drugs should be used for the management of SSc-related symptomatic motility disorders such as dysphagia, GERD, early satiety, bloating, pseudo-obstruction (58). Furthermore, experts recommend using intermittent or rotating antibiotics to treat symptomatic small intestine bacterial overgrowth in patients with SSc (59-60).

Comments on the guidelines

After reviewing all the above-stated topics together, some considerations are worth mentioning. Other therapies besides the previously listed ones have not been included due to the insufficient number of studies. Some further information has been published since the guidelines dissemination. This applies to:

a) Tocilizumab (162 mg/week subcutaneously) effective on the skin and lungs (61).

b) Mycophenolate mofetil compared to CYC in patients with SSc-ILD (62).

Lack of efficacy tests does not imply that efficacy is absent; thus the absence of a recommendation for a drug should not be interpreted as a contraindication for its use.

It is believed that these up-to-date recommendations will help improve the care of patients with SSc in an 'evidence-based' manner and may point to a direction for further clinical research.

Considering the complexity and heterogeneity of SSc and the limited evidence of the effectiveness of treatments, it is recommended that patients with systemic sclerosis be referred to specialized centers with appropriate management skills.

How I treat SSc: the experts' opinion-the Padua Experience

The therapeutic approach to patients with Systemic Sclerosis (SSc) should be tailored to their clinical manifestations and laboratory findings. First, it is important to define the subset of SSc (i.e., diffuse or limited cutaneous form) [63] and the ANA specificity (anti-centromere, anti-topoisomerase I, anti-RNA polymerase III) [64].

The limited cutaneous form is the most common subset of SSc and is characterized by acral localized skin lesions (hand sclerodactyly and “scleroderma facies”). The main clinical manifestations in this form are ischemic skin ulcers and subcutaneous calcifications. Gastrointestinal symptoms are often present at an early stage, while other visceral involvement is not frequent and slowly evolving. The only exception is pulmonary arterial hypertension, which affects approximately 10% of patients and can appear many years after SSc diagnosis [65].

The diffuse cutaneous form on the other hand is clinically characterized by rapidly evolving skin lesions, ischemic ulcers, concomitantinflammatory manifestations (e.g.arthritis, tendonitis and myositis), and frequent internal organ involvement (pulmonary fibrosis, cardiomyopathy, scleroderma renal crisis, gastrointestinal disorders), resulting in a poor prognosis for many patients [66].

Raynaud's phenomenon is the onset manifestation in about95% of SSc patients. Our first line treatment generally consists of oral vasodilators (especially calcium antagonists) at maximally tolerated dose [8], with the addition of intravenous iloprost therapy in case of severe Raynaud's phenomenon [25].

Cutaneous lesions in patients with diffuse SSc may spread within a few months from acrallocalized areas to almost the entire body surface, including the trunk. Given the

fundamental role that immune-mediated inflammation plays in the pathogenesis of these lesions, we recommend initiating immunosuppressive therapy as soon as possible with either methotrexate or mycophenolate mofetil [36, 67]. To potentiate the immunosuppressive therapy, SSc patients with rapidly progressive cutaneous involvement usually undergo long-term plasmaexchange in the Padua Rheumatology Unit [68] to “slow down” disease activity.

Ischemic ulcers affect nearly50% of SSc patients in both cutaneous forms. Intravenous iloprost is the only therapy that has proven to be effective in healing skin ulcers [69]. We recommend the use of antibiotics in case of ulcer superinfection. Treatment with the endothelin receptor antagonist bosentan may help prevent and reduce the onset of new digital ulcers in SSc patients [30,70].

Skin ulcers may also arise from subcutaneous calcifications which can reach a considerable size (“tumoral calcinosis”), most notably in patients with the limited cutaneous form. Various drugs, such as colchicine and diltiazem, have been tested as a treatment for calcinosis though with poor results. Tumoral calcinosis often requires surgery [71].

The gastrointestinal tract is the internal organ most frequently involved in SSc, notably the distal esophagus. GERD requires treatment with PPIs to reduce gastric acidity and prevent esophagitis [53,72]. Prokinetic (promotility) drugs such as domperidone and metoclopramide have shown poor efficacy in alleviating GI symptoms (dysphagia, early satiety, abdominal distension, persistent constipation) [73]. Antibiotic rotation is very

useful in preventing bacterial overgrowth which can cause recurring diarrhea and malnutrition in SSc patients [74].

The past fifteen years have seen the advent of new drugs offering substantial improvements in the treatment of PAH symptoms and hemodynamics [75]. Administration of the drugs requires a definitive diagnosis of PAH by cardiac catheterization. These novel agents include endothelin receptor antagonists, PDE5 inhibitors, prostacyclins and recently, riociguat (soluble guanylate cyclase stimulator) [76]. The NYHA functional class of the patient determines the choice of treatment (e.g. patients in class IV NYHA show a significant response only to continuous infusions of prostanoids) [18]. In our recent experience, macitentan (an endothelin receptor antagonist) is the treatment of choice for patients *in classes II and III NYHA* [31].

ILD remains one of the main causes of mortality in SSc, especially in patients with the diffuse form [77]; therefore treatment with immunosuppressive drugs ought to be initiated in the early inflammatory stage (alveolitis) to prevent the deterioration of lung function. We currently prefer mycophenolate mofetil over cyclophosphamide owing to the toxicity of the latter [39,78]. Stem cell transplantation procedures are only performed in few specialized centers now [46]. In case of poor clinical response or intolerance, patients with ILD are switched to rituximab, a specific anti-CD20 monoclonal antibody [79]. Rituximab also appears to be effective in treating chronic arthritis, another possible complication in patients with diffuse cutaneous SSc.

Cardiomyopathy, another visceral complication of diffuse SSc, should be treated even in its asymptomatic phase. However, early diagnosis is challenging and requires cardiac

MRI. The therapeutic approach is similar of ILD and includes immunosuppressants such as cyclophosphamide, azathioprine or rituximab [80,81].

Scleroderma renal crisis is a rare organ involvement characterized by rapidly progressive kidney failure that may result in patients requiring dialys is within few weeks. The therapy is based on the use of maximum tolerated doses of ACE inhibitors to reduce over-activation of the renin-angiotensin system, to control arterial hypertension and to prevent dialysis [47]. SRC can be triggered by vasoconstrictors such as calcineurin inhibitors or corticosteroids at high doses, and their use should therefore be avoided altogetherin scleroderma patients [49]. The therapeutic protocol for SRC that is performed in the Padua Rheumatology Unit consists of a combination of high dose ACE-inhibitors coupled with repeated plasma-exchange sessions, especially when it is complicated by renal microangiopathic hemolytic anemiaand/or thrombocytopenia [82].

In conclusion, SSc therapy must be tailored to the patient based on the disease subset and organ involvement.

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