Translating ideas into progress in systemic sclerosis

The papers in this supplement to Rheumatology have addressed current knowledge of the pathogenesis of SSc and its associated complications, alongside practical issues of disease management. As our colleagues illustrate, the last 10 years of partnership and research have ushered in a new era of progress in the field of SSc. The expansion of our understanding of SSc pathophysiology has, in turn, led to the development of advanced therapies that have improved prognosis and survival. Despite this, considerable challenges remain in developing our understanding of this disease further and in managing patients with SSc.

Our current understanding

The pathogenesis of SSc is complex, and appears to involve the endothelium, fibroblasts and immunological mediators [1]. An early, and possibly initiating, event is endothelial cell injury, although the precise aetiology is subject to ongoing research. Although the vasculopathy in SSc shows organ-specific features, striking similarities have been observed in different organ manifestations, with ET-1 believed to be an important mediator in pulmonary arterial hypertension (PAH), digital ulcers and scleroderma renal crisis (SRC) [2]. ET-1 therefore represents an important molecular target for therapeutic intervention in the vascular manifestations of SSc [2].

The complex pathology of SSc is also reflected by the difficulties that are encountered in diagnosing, screening and treating the different organ manifestations of SSc. Given the potential for organ-specific manifestations to lead to a rapid clinical deterioration in patients, their early detection and prompt treatment is of vital importance [3]. Some manifestations of SSc are easier to diagnose than others. Skin manifestations, for example, typically affect almost all patients, despite the heterogeneity of SSc [4].

Skin manifestations are important to the initial diagnosis of SSc and its sub-classification into two principal disease subsets: lcSSc and dcSSc [4]. Differences exist between the limited and diffuse disease subsets, and include the speed of disease progression, and the extent and severity of skin and visceral involvement. Diffuse disease is generally considered to be the more severe of the disease subsets, and is associated with a more rapid onset [4]. Cutaneous symptoms are often associated with, or preceded by, RP, an episodic digital ischaemia provoked by cold or emotional stress, symptoms are often associated with, or preceded by, RP, an episodic digital ischaemia provoked by cold or emotional stress.

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Patients in both subsets may also develop ischaemic digital ulcers. Digital ulcers are a major clinical problem in SSc, affecting >30% of the patients each year and causing substantial morbidity [5]. Vasodilators, such as α-adrenergic inhibitors, angiotensin receptor blockers, angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers, may improve the digital circulation [6]. Controlled data supporting these agents specifically in the treatment of digital ulcers are, however, limited. The recent, multicentre, randomized, double-blind, placebo-controlled QUINS trial investigated the effects of the long-acting ACE inhibitor, quinapril, in patients with lcSSc. No treatment effect on digital ulcers or on any other microvascular manifestations of lcSSc were observed [7].

Data from small studies suggest that intermittent treatment with the prostanooids epoprostenol and iloprost may improve healing of digital ulcers and prevent episodes of digital ischaemia [8–10], although controlled trials to specifically investigate their effects on digital ulcers are lacking. The phosphodiesterase-5 inhibitor sildenafil may also be beneficial for patients with digital ulcers [11]. The approval (in Europe) of the dual ET-1 receptor antagonist bosentan for the prevention of new digital ulcers in patients with SSc and ongoing digital ulcer disease means there is new hope for these patients [5, 12, 13].

For the identification of less overt manifestations of SSc, the use of screening strategies may be beneficial, particularly for organ-based complications that remain subclinical in their early stages [3]. Critical to the success of such an approach is the formation of strong collaborative links between colleagues in different disciplines, to increase their awareness of the necessity to monitor SSc patients [5]. The establishment of disease registries may also be beneficial; as demonstrated by the multicentre ItinerAIR Sclerodermie study in France [14].

In the ItinerAIR Sclerodermie study, SSc patients were subject to a screening algorithm for SSc-related PAH in order to assess its prevalence, the profile of diagnosed patients and the clinical relevance of potential diagnostic criteria [14]. Patients enrolled in this registry also formed the basis for a subsequent description of the natural history of ischaemic digital ulcers in SSc [15]. The establishment of disease registries may therefore facilitate longitudinal observation of trends in disease presentation, management and outcome [3].

One of the key observations of the ItinerAIR Sclerodermie study was the identification of SSc patients who exhibited mild PAH at an early stage [14]. This is of fundamental importance, as pulmonary manifestations, such as PAH, are leading causes of disease-related morbidity and mortality in SSc [16]. These findings exemplify the importance of regular screening for organ-based manifestations of SSc—not only for PAH—to identify early organ-based disease manifestations [16–18]. PAH has a dramatic impact on prognosis and survival, therefore annual echocardiographic screening for PAH is recommended for all patients with SSc, supported by right heart catheterization for confirmation of diagnosis [16]. A number of treatments are available for SSc-related PAH, which target the prostacyclin-, endothelin- and nitric oxide-mediated pathophysiological pathways [16]. Current data also suggest there is a strong rationale for early intervention, and for combining treatments that target different pathophysiological pathways with the aim of optimizing treatment response [16].

For physicians managing patients at risk of SSc-related interstitial lung disease (ILD), there are different clinical questions. Of key importance here is the detection and identification of clinically significant pulmonary fibrosis, and selection of an appropriate therapeutic strategy [17]. The combined evaluation of extent of disease using high-resolution CT and estimated pulmonary function test results is considered the most suitable means to guide diagnosis [17]. Pulmonary function test results have also proven useful in monitoring disease progression [17]. Treatment options for SSc-related ILD are currently limited to immunosuppressive agents or, in cases of end-stage disease, lung transplantation [17]. Regimens of oral or intravenous cyclophosphamide plus low-dose prednisolone have shown promise in stabilizing pulmonary function, although their use must be reconciled with an associated long-term risk of adverse events [17]. With the exception of one study, however, no patient included in retrospective or prospective studies with cyclophosphamide was selected on the basis of progression of ILD [19]. Since only a minority of patients with SSc develop severe ILD, Bérezné and colleagues [19] have proposed that further studies evaluating cyclophosphamide should instead focus on the subgroup of SSc patients with worsening ILD.
SRC represents a serious and life-threatening manifestation that affects ~5–10% of patients with SSc [20]. SRC is defined by an abrupt onset of hypertension and acute renal failure, which is associated with poor long-term survival. Historically, mortality among patients who developed SRC was very high, although current treatment regimens have reduced this to an estimated 24% [20–22]. Patients at greatest risk of developing SRC have been identified to be those with early diffuse disease, rapidly progressive skin disease, RNA polymerase-specific ANA and previous treatment with high doses of corticosteroids [20]. For patients who develop SRC, early and aggressive therapy with ACE inhibitors, supplemented with other anti-hypertensive agents if required, is essential [20].

Far more common manifestations of SSc are those which affect the gastrointestinal (GI) tract, causing considerable morbidity, impairing quality of life, and reducing survival. GI manifestations impact directly on motility, digestion, nutrient absorption and excretion, as a result of progressive histological lesions similar to those found in other organs [23]. Patients may experience dysmotility of the stomach, small intestine, colon and rectum—all of which can be responsible for severe and distressing symptoms. At present, there are few therapeutic options specific for the treatment of GI manifestations, with palliative therapy representing a treatment goal. It is therefore particularly important to carefully monitor and manage SSc patients with GI manifestations to minimize further degeneration and maximize quality of life [23].

The majority of patients with SSc are believed to be susceptible to cardiac manifestations, although early cardiac complications, if apparent, may progress subclinically. When apparent, cardiac manifestations can occur suddenly and be associated with very poor prognosis; however, the overall mortality of cardiac manifestation is relatively low [24]. Close monitoring of patients with clinically apparent symptoms is highly recommended, and there may be value in the monitoring of concentrations of the N-terminal portion of pro-B-type natriuretic peptide [24]. At present, there are few therapeutic options for patients with cardiac manifestations of SSc, although calcium channel blockers and ACE inhibitors may improve myocardial function [24].

CTDs including SSc and SLE are also commonly associated with vasculitis [25]. The diagnosis and management of vasculitis is reliant upon accurate clinical classification, but general symptoms can include fever, asthenia and weight loss. Systemic manifestations of vasculitis can arise, affecting the kidneys, lungs, GI tract, heart, or the musculoskeletal or nervous systems. While the exact pathogenesis of vasculitis in SLE remains unclear, thrombosis and inflammation of the endothelium are known to exist [25]. In addition, vasculitis and thrombosis are two pathological mechanisms that have been proposed to underlie development of PAH in patients with SLE [25]. In contrast to patients with SSc, patients with SLE and other CTDs who develop PAH may respond well to immunosuppressive therapy. For patients with necrotizing vasculitides, treatment with cyclophosphamide and corticosteroids may be beneficial. Maintenance therapy using channel blockers and ACE inhibitors may improve myocardial function [24].

The next 10 years

Improving the standard of care for SSc patients will remain a treatment goal for the foreseeable future. As a result of the significance and diversity of organ-based manifestations in SSc, a continued need will exist for increased collaboration between healthcare professionals in all relevant fields. The establishment and maintenance of interdisciplinary networks will be necessary to facilitate future learning and optimize patient management. An increased appreciation and awareness of the clinical complications will benefit our colleagues, and will be fundamental to facilitating timely and appropriate intervention.

Continued research to develop our understanding of the molecular and cellular mechanisms underlying SSc pathogenesis has already identified common pathogenic mechanisms, and will continue to facilitate a more global and comprehensive management of SSc in the future. A diverse multitude of prototypical targets that includes cytokines, growth factors, vasoactive mediators and cellular targets has already been uncovered [26]. Future progress will clearly hinge on continued pre-clinical research and robust, controlled clinical trials to investigate potential therapies [26].

With continued research into the pathogenic mechanisms underlying SSc and by increasing the profile and knowledge of this disease within the medical community, patients with SSc can ultimately look forward to improved clinical outcomes in the future. As a result of the last 10 years of partnership in SSc, the future outlook has never been brighter.

References

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