Advances in pathogenesis and treatment of systemic sclerosis

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ABSTRACT

Systemic sclerosis is the most severe disease within the scleroderma spectrum and is a major medical challenge with high mortality and morbidity. There have been advances in understanding of pathogenesis that reflect the interplay between immune-inflammatory processes and vasculopathy and fibrosis. It can be regarded as a disease of connective tissue repair and this leads to organ-based complications. However the aetiology and triggering events remain to be elucidated. Treatment is available for many aspects of the disease although the available therapies are not curative and some complications remain very challenging, especially non-lethal manifestations such as fatigue, calcinosis and anorectal dysfunction. Immunosuppression is now established as a beneficial approach but balancing risk and benefit is vital, especially for powerful approaches such as autologous stem cell transplantation.

KEYWORDS: Scleroderma, systemic sclerosis, fibrosis, pulmonary hypertension and autoantibodies

Introduction

Systemic sclerosis (SSc) is an autoimmune rheumatic disease with high case-specific mortality. More than half those diagnosed with SSc eventually die as a direct result of the disease. Moreover, in addition to high mortality from internal organ disease there is also a very substantial non-lethal burden that impacts on function, quality of life and causes a range of severe and disabling symptoms.

The range of organ-based complications is shown in Fig 1. These occur at different time and frequency in the two major subsets of SSc, limited and diffuse disease. The timing and frequency of major heart, lung or kidney involvement has recently been defined in a large single-centre cohort.[1] This is helpful in defining the risk of each of these important manifestations. The clinical heterogeneity of SSc is important since it determines the appropriate approach to treatment. An overview of treatment approaches is given in Fig 2.

Over the past few years there have been substantial advances in the understanding of SSc and also in the assessment and
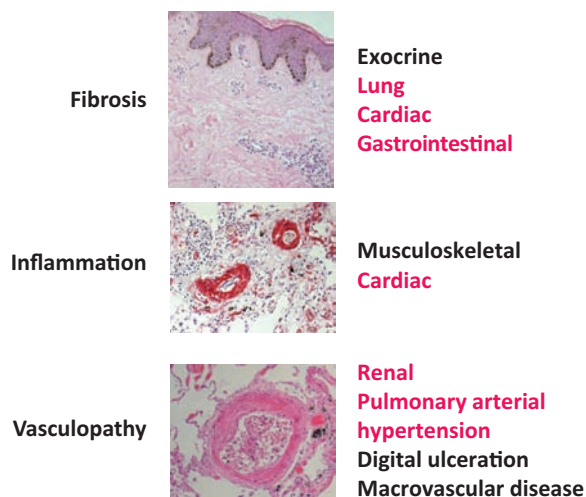

Fig 1. Pathology and clinical impact of SSc. The hallmark pathologies of fibrosis, inflammation and vasculopathy in SSc translate into a challenging array of organ-based complications that define the burden and impact of disease. Highlighted in red are those aspects that contribute to high case-specific mortality, mostly due to cardiorespiratory manifestations. SSc = systemic sclerosis.

management of the disease. Overall survival has improved and this probably reflects earlier detection of major complications, as well as a more proactive approach to management of the condition. [1]

## Current paradigm for SSc pathogenesis

It is now appreciated that SSc is an autoimmune disease and shares much in common with other similar conditions. There is activation of the innate and adaptive immune systems. A range of disease specific autoantibodies are important for diagnosis and help to stratify distinct patient groups. Vascular manifestations are associated with the immunoinflammatory aspects of the disease; these include microvascular

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Fig 2. Overview of management of SSc. Patients with a confirmed diagnosis of SSc are classified into diffuse or limited subsets and this determines the main focus of therapy although around one fifth of cases have overlap features of another concurrent autoimmune rheumatic disease. In all cases vigilant follow up to identify major complications and general symptomatic approaches are cornerstones of modern management. dc = diffuse systemic sclerosis; GI = gastrointestinal; lcSSc = limited systemic sclerosis; SSc = systemic sclerosis.
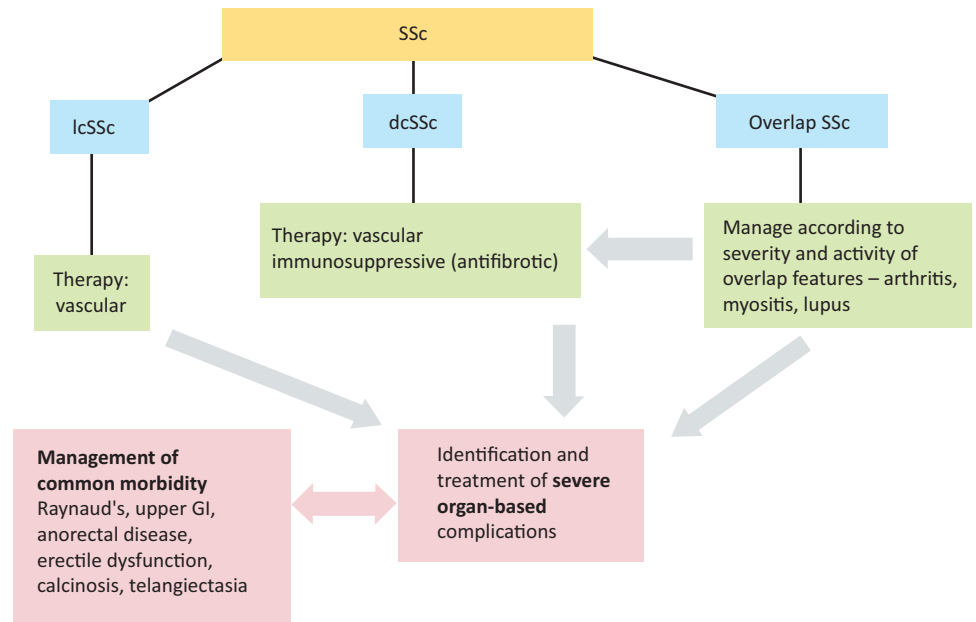
abnormalities, with activation of endothelial cells and macrovascular changes, including proliferative vasculopathy. In addition, a propensity to cold or stress-induced vasospasm is typical in SSc and manifests as Raynaud's phenomenon. This is a common finding in other autoimmune rheumatic diseases and also in otherwise healthy individuals, when it is termed primary Raynaud's phenomenon.[2]

It is notable that recent genetic studies of SSc have identified a number of loci associated with the disease or with subsets or complications.[3] Association with antinuclear antibody (ANA)-based subgroups have consistently been more reproducible than those for non-immune genetic loci across different patient cohorts. Many of these loci are relevant to innate immune system function although some may reflect altered connective tissue synthesis or remodelling, such as a reported polymorphism in the connective tissue growth factor promoter associated with SSc.[4]

An emerging model of pathogenesis is that SSc represents a susceptibility phenotype to excessive fibroproliferative response to tissue injury or damage that may be modulated or driven by the immune response, but appears to become sustained and independent of significant ongoing inflammation.[5] The differing extents of skin disease that define major SSc subsets could be determined by host factors, and the pattern of internal organ disease may reflect costimuli or other factors. This model fits especially for complications such as scleroderma renal crisis (SRC) or pulmonary arterial hypertension, where only a minority of cases are affected and there is a clear temporal element to risk. This is exemplified by recent studies confirming the association between malignancy and SSc in some cases,[6] suggesting shared pathogenic factors or a link with autoimmunity.[7] Thus, SRC seems to develop mostly within three years of disease onset, but in later stage disease is very rare, suggesting that the majority of SSc cases may be protected from SRC. Pulmonary hypertension (PAH) develops in 1–2% of SSc cases per year from three years of disease duration; this risk persists with prevalence at approximately 5% at 5 years, 10% at 10 years and 15% at 15 years.[8]

Recent animal model studies[9,10] have better defined the potential mechanisms for the association in PAH, revealing that SSc may represent a phenocopy of bone morphogenetic protein receptor type II (BMPRII) deficiency that reflects transforming growth factor beta induced promotion of BMPRII protein degradation.[11]

Better understanding of the pathogenesis of SSc also has unravelled likely pathways and mediators that could drive the disease. Some of the pathways and mediators are summarised in Fig 3. Improved understanding of the pathogenesis of SSc is important since some of these pathways may be amenable to therapeutic modulation.

Classification and subsets of SSc

Traditional classification of SSc has depended on the extent of skin sclerosis. This defines cases of diffuse or limited disease. Other relevant subsets include cases labelled as SSc sine scleroderma. These are patients that manifest SSc-related internal organ disease, Raynaud's phenomenon and have typical ANA reactivity but lack skin sclerosis. Such cases are likely to often be diagnosed as organ-specific conditions, such as idiopathic lung fibrosis, PAH or primary gut dysmotility syndromes. It is important to recognise these cases as additional investigation, and management may be necessary. Another important group are those cases of SSc with overlap connective tissue disease (CTD). These may include some cases of mixed CTD although this disease has more defined classification criteria. Up to one-fifth of cases of SSc will have features of arthritis, lupus or myositis, and these cases need to receive treatment for the overlap manifestations as well as SSc.

The classification criteria for SSc were updated in 2013 and the new criteria[12] are proving substantially more robust that previous American Rheumatism Association (ARA) preliminary criteria.[13] The new system reflects contemporary assessment and investigation of SSc. The current classification criteria are listed below and for a definite case to be identified at least 9 points are
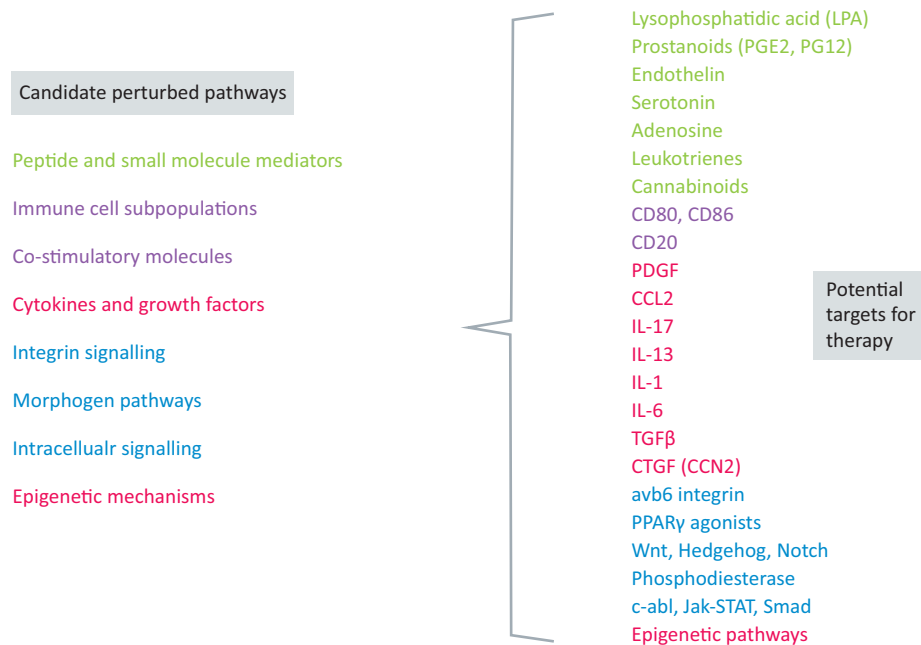
Candidate perturbed pathways	
Peptide and small molecule mediators	Lysophosphatidic acid (LPA)
	Prostanoids (PGE2, PG12)
	Endothelin
	Serotonin
	Adenosine
	Leukotrienes
	Cannabinoids
Immune cell subpopulations	CD80, CD86
Co-stimulatory molecules	CD20
	PDGF
Cytokines and growth factors	CCL2
	IL-17
	IL-13
	IL-1
	IL-6
	TGFβ
	CTGF (CCN2)
Integrin signalling	avb6 integrin
Morphogen pathways	PPARγ agonists
	Wnt, Hedgehog, Notch
Intracellualr signalling	Phosphodiesterase
	c-abl, Jak-STAT, Smad
Epigenetic mechanisms	Epigenetic pathways

Potential targets for therapy

Fig 3. Disease mechanism in SSc: linking pathogenesis to therapeutic targets. Studies of patient samples, genetics and animal models have defined likely processes that determine the pathogenesis of SSc. Within these pathways there are candidate mediators that may be targeted in future therapeutic trials. Some of these such as endothelin axis and IL6 are already in the clinical arena.

required. It should be noted that all cases that fulfil the older ARA criteria are within this new system, however it is designed to be more sensitive for cases with organ-based pathology or limited disease. It is important to clarify that the classification criteria are not sensitive enough to confirm diagnosis in all cases and also that they do not apply when there is an alternative medical condition, such as another autoimmune rheumatic disease, that better explains the observed clinical features.

Utilising autoantibody patterns in SSc classification

One of the strongest signals of autoimmunity being relevant to SSc is the association of high-titre SSc patterns of ANA reactivity, which point towards specific alterations in the adaptive immune system. These include several SSc-specific reactivities and these are generally mutually exclusive. This has allowed association studies to define the risk of specific complications, and these associations are useful in clinical practice, especially as their hallmark SSc antibody is usually present at time of diagnosis and this remains constant during follow up. Specific clinical associations are listed in Table 1 and these are generally independent of disease subset. In this way, the ANA patterns provide an alternative and complementary subgrouping for SSc that is clinically relevant. Interestingly, many of the genetic associations with SSc, especially those relating to immunogenetics, are strongly associated with ANA subtypes. This may reflect the defined MHC class II associations for individual ANAs that likely determine the immunoreactivity to relevant target epitopes. Ultimately, this may inform therapeutic advances.[14]

Disease-modifying treatment

Although there is no curative therapy for SSc, there has been substantial progress in treatment over the past decades. This includes better evidence to support standard approaches to treat the immune and vascular aspects of SSc. There are no proven antifibrotic treatments, although potential therapies are emerging and under evaluation. It is encouraging, by analogy, that two agents have recently been licensed for treatment of lung fibrosis in IPF. Otherwise, the majority of therapeutic advances in SSc have come from better identification and management of specific organ-based complications.

Broad spectrum immunosuppression

A number of trials have now confirmed benefit from immunosuppression, demonstrating improvement in skin or stabilisation of lung function using agents such as cyclophosphamide or methotrexate. The best current evidence for effectiveness of a broad spectrum approach comes from emerging data in high-intensity immunosuppression with autologous haemopoietic stem cell transplantation. Two trials are published, the small ASSIST study from the USA[15] and a much larger ASTIS trial led from Europe.[16] A third study, SCOT, is North American and has fully recruited and is ongoing.[17] The most complete dataset so far is ASTIS. This study suggested improved long-term survival and event-free survival after autologous stem cell transplant, compared with a control arm receiving intravenous cyclophosphamide. However, survival advantage was not seen until two years after transplant and a 10% transplant-related mortality (TRM) was reported. Improvement in secondary end-points, such as skin, offered more robust evidence of benefit. However, this remains a challenging study to translate into practice due to the high TRM and the need to exclude candidates at very high risk of cardiopulmonary disease due to unacceptable mortality. Less toxic treatment approaches and better case selection methods will be important to progress in this field. Nevertheless, the ongoing studies, in particular ASTIS, have been landmarks in

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Table 1. Summary of patterns of ANA reactivity and clinical and genetic associations in systemic sclerosis.

Target antigen	Frequency, %	Staining pattern	Clinical association	Genetic association*
Centromere	15–40	Kinetochore	lcSSc, PAH	HLA-DQB1
				TNF-863A
				GRB10
				NOTCH4
Topoisomerase-1 (Scl70)	10–40	Speckled	dcSSc, lung fibrosis	HLA-DPA1/B1
				HLA-DPB2
				HLA-DRB1
RNA polymerase III	4–25	Fine speckled/nucleolar	Renal crisis, malignancy, PAH	HLA-DRB1
				HLA-DRB3
				HLA-DRB4
				HLA-DQB4
				EDNRA
Fibrillarin (U3RNP)	1–5	Nucleolar/coilin	PAH, cardiac, myositis	HLA-DQB1
Pm-Scl	3–6	Nucleolar	Myositis overlap	None reported
U1RNP	5–35	Speckled	Overlap features	HLA-DRB1
				HLA-DPB1
Th-To	1–7	Nucleolar	lcSSc, PAH, lung fibrosis	None reported
U11/U12	1–5	Nucleolar	Lung fibrosis	None reported

*the table summarises reported associations that may differ between ethnic and geographically defined populations but are consistently seen for HLA region and specific ANA patterns suggesting that there is a genetic basis to the development of SSc-associated autoantibodies. ANA = antinuclear antibodies; dcSSc = diffuse systemic sclerosis; HLA = human leukocyte antigen; lcSSc = limited systemic sclerosis; PAH = pulmonary arterial hypertension.

the field of SSc treatment and provide a robust platform for future progress.

Although less robust than a prospective controlled trial design, observational and cohort studies have emerged that suggest benefit from currently used immunosuppressive drugs. The UK observational study suggested improvement with all three of the agents in common use for skin fibrosis, methotrexate (MTX), mycophenolate mofetil (MMF) and cyclophosphamide.[18] However, it was not sufficiently powered to discriminate between these agents. A large European observational trial in early diffuse SSc is underway[19] and may provide important information. Analysis of small controlled trials of MTX and cohort studies of MMF are also supportive of benefit for these agents in SSc and this has been incorporated into the current European League Against Rheumatism treatment recommendations.[20]

Vascular therapies

SSc is as much a vascular disease, as a fibrotic process and all patients should be considered for treatment of vasculopathy. This includes treatment of secondary Raynaud's phenomenon, as well as the complications of digital vasculopathy, including digital ulceration and gangrene. A multifaceted approach is needed that includes multidisciplinary input to optimally manage digital vascular disease. Other vascular complications, such as pulmonary arterial hypertension or scleroderma renal crisis, occur less often but are treatable; management is discussed further below.[21]

Management of organ-based disease

Lung fibrosis

Management of lung fibrosis requires careful assessment. Serial pulmonary function testing and definition of the extent of disease by lung computerised tomography (CT) scan provide the cornerstone of management. A simple staging system has been developed and validated in several independent cohorts. This offers a practical tool for identifying cases that are at greatest risk of progression to severe lung fibrosis and that should be treated with more intensive immunosuppression. The evidence base for using cyclophosphamide in lung fibrosis comes from two clinical trials. The US study, SLS1, suggested statistical benefit at 12 months for oral cyclophosphamide compared with placebo; however this benefit was very marginal. Benefit was maximal at 18 months after starting therapy and was particularly apparent in cases with more extensive disease on CT scan.[22,23] The UK trial of intravenous cyclophosphamide suggested similar treatment effect, albeit as a strong trend, after 6 months of intravenous therapy followed by oral azathioprine.[24] The SLS2 trial is underway to compare MMF with oral cyclophosphamide. In relation to skin disease, there is an emerging evidence base from small trials and cohort analysis supporting MMF use. Rituximab has also been used as a therapy for severe lung fibrosis and will be tested in prospective clinical trials that are planned or ongoing. At present, rituximab is reserved for use in cases that have failed to respond adequately to standard immunosuppression. Management of oesophageal reflux is important in SSc

to minimise risk of aspiration-associated lung damage. Antioxidant agents, including *N*-acetyl cysteine, are plausible and often used in progressive disease. The utilisation of recently licensed IPF drugs, such as pirfenidone and nintedanib, remains uncertain but will hopefully be addressed in future clinical trials.

Pulmonary hypertension

Diagnosis of PAH can only be made by right heart catheter.[25] It occurs in 1–2% of SSc cases per year and this risk appears to persist throughout the disease. It is therefore an important complication that may occur in up to 15% of cases.[8] It most often reflects precapillary PAH and is treatable using licensed therapies for group I PAH. In SSc-associated PAH treatments are available as a result of CTD-PAH subjects being included in all the pivotal trials that have led to licensing of current treatments.[26] Generally a drug targeting the nitric oxide pathway is used or an endothelin receptor antagonist; later, these oral agents are often given in combination. Prostanoid therapy is mostly given to more advanced or progressive cases since administration is more challenging. In SSc, approximately one-third of PH is due to associated cardiac disease I (group II postcapillary PH) or severe lung fibrosis with hypoxia (group III PAH). Lung fibrosis and PAH often co-exist making management challenging. Therefore, expert assessment is needed to determine whether there is a PAH component that may be amenable to treatment.[27]

Scleroderma renal crisis

SRC is treatable using angiotensin-converting-enzyme inhibitors and these have transformed outcomes.[28] Awareness of risk and patient education are important and enable SRC to be diagnosed as soon as possible. Early diagnosis is associated with better long-term outcomes in terms of renal recovery and survival. Since renal recovery may occur up to two years after SRC, decisions about renal transplantation should be delayed until this time, although allografting is certainly a benefit for patients on long-term dialysis and associated with improved survival and quality of life.[29] Recurrent renal crisis in the allograft is very rare and this may reflect the obligate immunosuppression used in this context after grafting that may also treat the underlying SSc.[30]

Gastrointestinal complications

The commonest internal organ complication of SSc is involvement of the gastrointestinal tract.[31] Almost all patients have troublesome gastro–oesophageal reflux but this generally responds well to treatment with acid suppressive drugs, especially proton pump inhibitors. These may be needed as long-term therapy and administered at higher doses than in general medical practice. A combination of protein-pump inhibitors and H_2 antagonists may give additional symptom relief. Additional common gut complications in SSc include constipation, anorectal incontinence and small intestinal overgrowth. The latter may be treated using broad spectrum antibiotics.[32] In a minority of cases, intestinal failure occurs and there is a growing experience of using parenteral nutrition at home to improve the outcome of this subgroup of SSc cases.[33]

Other difficult aspects of disease

There are many aspects of SSc that remain challenging to patients and are hard to treat. This includes severe pruritus, calcinosis, fatigue, and the impact on facial appearance and musculoskeletal function. The non-lethal burden of SSc is becoming more important as survival improves as a result of better management of some of the life-threatening complications. Therefore, the challenge of SSc is likely to remain despite advances in management that are occurring.[34]

Conclusions

SSc is a heterogeneous disease and the diverse patterns of clinical involvement require an individualised approach to management. Subsetting and staging the disease is important but more specific risk stratification is also needed. As discussed, ANA pattern can be used to predict risk of specific complications, in particular lung fibrosis (anti-topoisomerase-1) or SRC (anti-RNA polymerase). Composite scores to predict PAH development (DETECT and others) and also lung fibrosis and survival[8,35–37] are also emerging. These scores often integrate multiple clinical and laboratory features and, once validated, offer potential for a stratified approach to treatment that may further improve outcome. ∎

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