Systemic sclerosis

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Systemic sclerosis, also called scleroderma, is an immune-mediated rheumatic disease that is characterised by fibrosis of the skin and internal organs and vasculopathy. Although systemic sclerosis is uncommon, it has a high morbidity and mortality. Improved understanding of systemic sclerosis has allowed better management of the disease, including improved classification and more systematic assessment and follow-up. Additionally, treatments for specific complications have emerged and a growing evidence base supports the use of immune suppression for the treatment of skin and lung fibrosis. Some manifestations of the disease, such as scleroderma renal crisis, pulmonary arterial hypertension, digital ulceration, and gastro-oesophageal reflux, are now treatable. However, the burden of non-lethal complications associated with systemic sclerosis is substantial and is likely to become more of a challenge. Here, we review the clinical features of systemic sclerosis and describe the best practice approaches for its management. Furthermore, we identify future areas for development.

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Introduction

Systemic sclerosis is an immune-mediated disease that represents a major clinical challenge for physicians and patients. Systemic sclerosis has a high mortality—greater than any other rheumatic disease—despite evidence of improved survival, especially for patients with diffuse cutaneous systemic sclerosis.[1,2] For the patient, systemic sclerosis is associated with great uncertainty of outcome and development of manifestations that are potentially lethal or can reduce quality of life. Systemic sclerosis is uncommon and is designated an orphan disease with a high unmet medical need.[3–5] Diagnosis can often be delayed, which adds to the patient burden. Although some excellent resources for patient education are available (for example, Scleroderma & Raynaud's UK), abundant negative information is also available, especially on the internet, which can increase the concern and anxiety of patients and family members once the diagnosis of systemic sclerosis has been made.

For clinicians, initial concerns might be similar to patient concerns, but, since systemic sclerosis is an uncommon disease for most physicians, the implications of a new diagnosis might be shaped by limited experiences of the disease. Even at expert centres, challenges exist around making the diagnosis and determining the extent of disease and activity (ie, rate of disease worsening), which might affect decision making about treatment.[6,7] A major challenge is stratification of risk of future complications. Although clinical and laboratory tools exist and are being developed and refined, stratification and individualised treatment of systemic sclerosis remain important and unattained aspirations.[8] Management of cases of systemic sclerosis according to evidence-based and expert recommendations, and with involvement of appropriate expert centres, is important.

Clinical presentation

Although certain cardinal manifestations, such as Raynaud's phenomenon and gastro-oesophageal reflux,[9,10] often present early in the disease, the early clinical signs of systemic sclerosis can be varied. However, these symptoms are also very common in the general population, so it is important that any assessment takes account of specific features that might indicate a diagnosis of systemic sclerosis and considers them in the clinical context (ie, disease stage and subset and anti-nuclear antibody [ANA] profile).[11] Some patients present with inflammatory skin disease, puffy and swollen fingers, musculoskeletal inflammation, or constitutional manifestations such as fatigue.[12] In some patients, organ-based manifestations of the disease are observed, which might include lung fibrosis, pulmonary arterial hypertension, renal failure (usually with accelerated-phase hypertension and a thrombotic microangiopathy clinical picture), or gastrointestinal complications.[13,14]

Presentation of patients to the emergency room or non-specialist clinics can delay the ultimate diagnosis of systemic sclerosis and compromise appropriate treatment and investigation.[1] Once systemic sclerosis is suspected, patients should be assessed so that a definite diagnosis can be ascertained. Making a definitive diagnosis will usually involve fulfilment of the 2013 European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) classification criteria (panel 1),[15,16] although, given that these criteria are for classification, not all patients diagnosed with systemic sclerosis will

For **Scleroderma & Raynaud's UK** see https://www.sruk.co.uk

Search strategy and selection criteria

We searched PubMed (January, 1990, to November, 2016) using the search terms "systemic sclerosis" or "scleroderma" in combination with the terms "management", "classification", "pulmonary", "renal", "cardiovascular", and "epidemiology". We largely selected publications from the past 5 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Priority was given to primary research publications and randomised trials when discussing interventional aspects. Review articles and book chapters are cited to provide readers with more detail and additional references.

Panel 1: **Summary items from the 2013 American College of Rheumatology and European League Against Rheumatism criteria for the classification of systemic sclerosis***

Proximal skin involvement
- Skin thickening of the fingers of both hands, extending proximal to the metacarpophalangeal joints (sufficient criterion; score 9)

Skin thickening of the fingers (only count the higher score)
- Puffy fingers (score 2)
- Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints; score 4)

Fingertip lesions (only count the higher score)
- Digital tip ulcers (score 2)
- Fingertip pitting scars (score 3)

Telangiectasia (score 2)

Abnormal nailfold capillaries (score 2)

Pulmonary arterial hypertension or interstitial lung disease (maximum score of 2)
- Pulmonary arterial hypertension (score 2)
- Interstitial lung disease (score 2)

Raynaud's phenomenon (score 3)

Systemic sclerosis-related autoantibodies (maximum score of 3)
- Anti-centromere (score 3)
- Anti-topoisomerase I (score 3)
- Anti-RNA polymerase III (score 3)

*A total score of 9 is needed for a definite classification.

Panel 2: **Typical features of the major subsets of systemic sclerosis**

Limited cutaneous systemic sclerosis
- Distal skin sclerosis
- Long history of Raynaud's phenomenon
- Late-stage complications frequent
- Pulmonary arterial hypertension and severe gut disease frequent and serious

Diffuse cutaneous systemic sclerosis
- Proximal limb or trunk involvement, with skin sclerosis
- Short history of Raynaud's phenomenon
- Increased risk of renal crisis and cardiac involvement
- High frequency of severe lung fibrosis

Sine scleroderma
- Raynaud's phenomenon
- Typical systemic sclerosis serology or capillaroscopic features
- No skin thickening
- Organ-based or other vascular manifestations

Systemic sclerosis overlap syndrome
- One of the three subsets together with clinical and investigational features of another autoimmune rheumatic disease

fulfil them. These updated criteria are considerably more accurate for diagnoses than the previous ACR preliminary criteria from 1980.[17] Over the past 15 years, there has been a focus on early diagnosis.[18,19] Some of the key early clinical manifestations of systemic sclerosis are associated with development of early internal organ disease; however, the validity and utility of criteria to define patients with these features are, as yet, unknown.

Signs and symptoms

Multiple organ-based manifestations are a hallmark of systemic sclerosis and are important in the diagnosis and classification of the disease. In cases of diffuse disease, skin tightness and itching are early features.[20] Some patients present with musculoskeletal pain that might mimic inflammatory joint disease. Occasionally, other regional sensory symptoms are present, such as trigeminal or glossopharyngeal neuralgia or neuropathy. Lower-limb swelling and muscle weakness or fatigue might be reported, especially in early-stage diffuse cutaneous systemic sclerosis.[6] Weight loss, often associated with reduced appetite or food intake, and exertional breathlessness are common symptoms.[21] Presentation of these symptoms should prompt an urgent and thorough investigation to exclude cardiorespiratory complications that could require urgent treatment. Clinical examination allows major features of the external disease, as well as skin, vasculature, and musculoskeletal involvement, to be defined and assists in making a definite diagnosis. Organ-based complications require careful assessment.[7] Baseline investigations form part of the essential early investigation of systemic sclerosis.[22]

Differential diagnosis

The differential diagnosis of systemic sclerosis involves consideration of skin manifestations, vascular features, and organ-based complications. For the skin, it is important to consider other causes of skin or subcutaneous fibrosis, as well as other infiltrative skin diseases.[23] Other scleroderma-like diseases are an important consideration that might require expert assessment and treatment. Localised forms of scleroderma are usually distinct from systemic sclerosis but, occasionally, there can be confusion, especially for generalised morphea. Differential diagnosis of vascular features includes the many other causes of Raynaud's phenomenon, as well as other peripheral vascular diseases, especially vasculitis.[24] The urgent need to treat vascular insufficiency in some cases requires timely evaluation of the differential diagnosis. Expertise in evaluating patients with systemic sclerosis and reliable access to specialists in vascular-associated medicine are important. The inflammatory features of systemic sclerosis are included in the differential diagnosis of several other immune-mediated rheumatic diseases, including lupus, arthritis, and myositis, which complicates its differential diagnosis.[25] It is important to remember that up to 20% of patients with systemic sclerosis have features that overlap with connective tissue disease,[26] and diagnosis of

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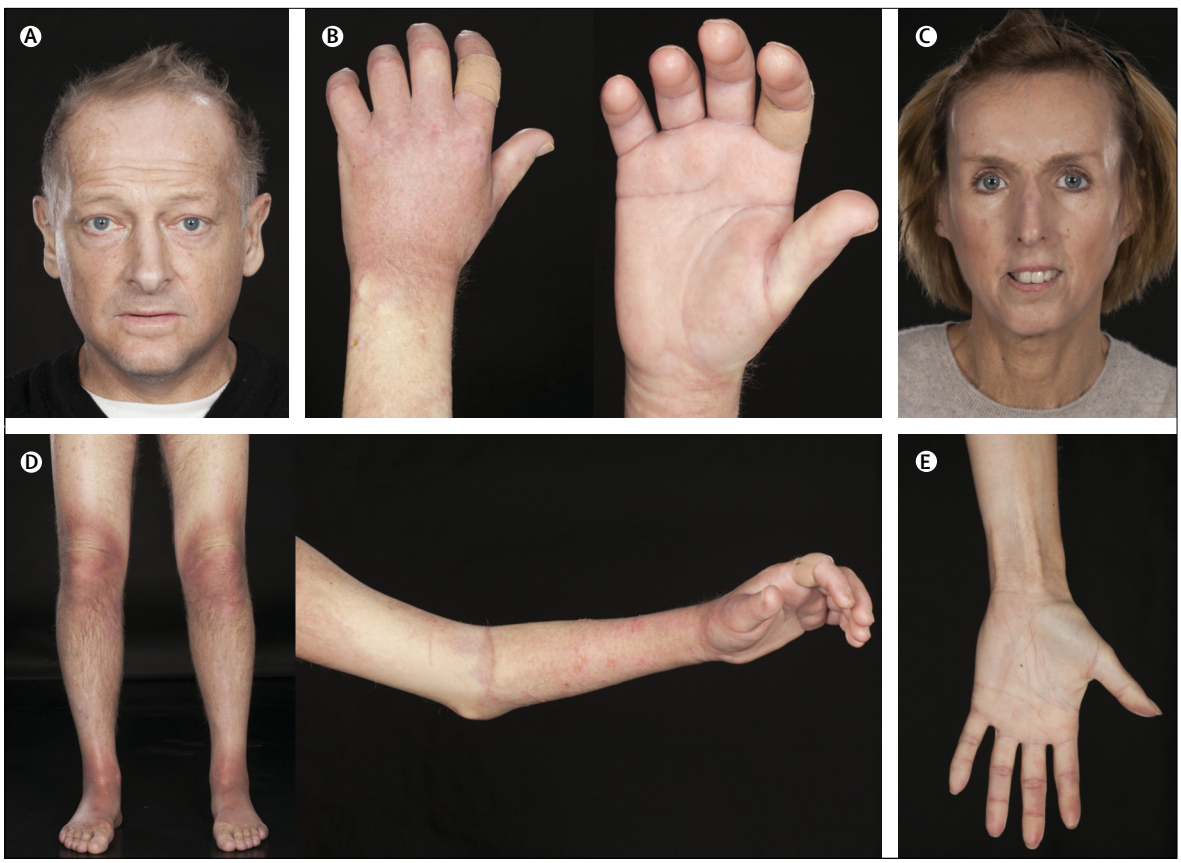

Figure 1: **Diffuse cutaneous systemic sclerosis**
(A) Severe skin involvement in diffuse cutaneous systemic sclerosis has an effect on facial appearance. (B) Hand function is affected in these patients and is often associated with severe digital ulcers and ulceration over areas of pressure or trauma. (C) Atrophic changes of late-stage diffuse skin involvement with prominent hair regrowth. (D) Typical blanching of indurated thickened, hairless skin over the length of the limbs is shown in a patient with early diffuse systemic sclerosis and anti-RNA polymerase antibody positivity. (E) Atrophic changes of the hands in late-stage diffuse skin involvement.

connective tissue disease does not exclude the concurrent diagnosis of systemic sclerosis. Capillaroscopy can differentiate between cases of isolated or primary Raynaud's phenomenon, which represents a common potential differential diagnosis for early systemic sclerosis.[27]

Subset classification

Cases of systemic sclerosis can generally be classified into one of two major disease subsets based on the extent of skin involvement (panel 2): those with proximal involvement are classified as diffuse cutaneous systemic sclerosis (figure 1), whereas those with restricted involvement affecting the limbs distal to the elbows or knees, with or without face and neck involvement, are classified as limited cutaneous systemic sclerosis (figure 2).[28] These skin-based subsets define the disease dichotomously and have other distinguishing clinical associations, as well as specific serum autoantibody profiles. However, some cases fall within the subsets less clearly, and ongoing initiatives aim to refine and improve the subset classification of systemic sclerosis. A small number (<5%) of patients have clinical features (most commonly Raynaud's phenomenon, digital ulcers, and pulmonary arterial hypertension) and autoantibodies that are specific to systemic sclerosis, but no skin involvement (so-called sine scleroderma).[29] Studies[30–32] suggest that ANA patterns and clinical features can be used for early identification of subsets, especially for patients who later develop diffuse systemic sclerosis. Systemic sclerosis overlap syndrome can be present in any of the three subsets, although it is most commonly found in patients with limited cutaneous systemic sclerosis.[33,34]

Clinical and laboratory science

Epidemiology, risk factors, and genetics

The aetiopathogenesis of systemic sclerosis is complex.[35] Globally, around one in 10 000 people are estimated to be affected by systemic sclerosis.[36] This small number suggests that the causal factors occur relatively uncommonly and, in complex disease, these factors probably include several environmental factors alongside genetic susceptibility.[37,38] Other factors, such as epigenetics, might also be important.[39–41] Twin studies[42] have been done to confirm the role of genetic factors in systemic sclerosis,

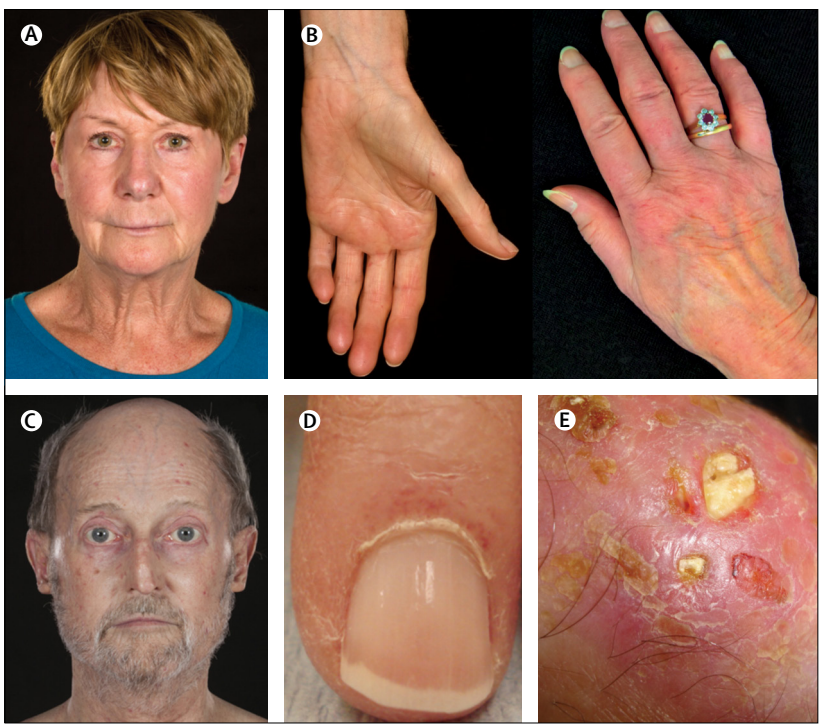

Figure 2: **Limited cutaneous systemic sclerosis**
Limited cutaneous systemic sclerosis is associated with mild skin involvement distal to the elbows and knees, with or without face and neck involvement, and sparing of the chest and abdomen. (A) Perioral soft tissue loss. (B) Sclerodactyly. (C) Facial telangiectasis. (D) Dilated nailfold capillaries. (E) Extensive calcinosis cutis.

although the rarity of twin pairs has limited this approach. Genetic association studies,[36] and more recent sequencing analysis,[43] have defined some factors that contribute to genetic susceptibility to systemic sclerosis and specific complications. Genetic factors might be important drivers of molecular and clinical diversity within systemic sclerosis. Identification of genetic factors involved in systemic sclerosis is important because many of these factors are shared with other autoimmune or immuno-inflammatory diseases, especially other rheumatic disorders.[44–46]

Case reports and series that associate certain organic chemicals or pesticides with the development of systemic sclerosis suggest that exposure to environmental chemicals might be relevant to some cases of systemic sclerosis.[47,48] However, more frequently, chemical exposure has been associated with scleroderma-like diseases that have some characteristics of systemic sclerosis but distinct clinical phenotypes. For example, some cases of scleroderma-like diseases have been associated with vinyl chloride monomer and various organic solvents.[46] Interestingly, HLA associations and hallmark autoantibodies of systemic sclerosis have been observed in some cases of vinyl chloride-associated disease.[46] Importantly, suspected environmental or chemical triggers of scleroderma-like diseases might also cause systemic sclerosis.[47,48]

Chemotherapy drugs, such as taxanes or gemcitabine, and radiotherapy can trigger systemic sclerosis or specific complications, which are important considerations in patients who have a concurrent malignancy and systemic sclerosis.[49] Although case series continue to identify silicone breast implants as a potential trigger of systemic sclerosis, and systemic sclerosis as a result of silicone breast implants might be a rare event in susceptible individuals,[50–53] no association has been found for silicone breast implants based on large epidemiological studies.[54,55] Other chemicals associated with scleroderma-like disorders include L-tryptophan and certain forms of gadolinium, an MRI contrast agent. Gadolinium was shown to trigger nephrogenic systemic fibrosis in some individuals with renal insufficiency,[55] although identification and avoidance of this trigger in these patients has virtually eliminated the occurrence of this disease.

Pathophysiology

Substantial progress in understanding the pathogenesis of systemic sclerosis has been made because of an increasing number of descriptive studies using modern molecular technologies and a more complete representation of the features of systemic sclerosis in preclinical mouse models of the disease. Additionally, the inclusion of biological sampling in clinical trials[56] is enabling reverse-translational studies that further refine the pathogenetic understanding of systemic sclerosis. Although systemic sclerosis is conventionally seen as a prototypical fibrotic disease within the family of autoimmune rheumatic disorders, this concept is likely to be an oversimplification.[57] A better paradigm is probably one of dysregulated or dysfunctional repair of connective tissue in response to injury. In this way, all constituents of tissue repair might be relevant to the disease, which opens up new avenues for treatment.

This paradigm of dysregulated or dysfunctional repair of connective tissue involves a mosaic of cell types and processes. A traditional focus on a tripartite pathogenesis[58] (linking vascular, immune, and mesenchymal components) is of value but is also limited by not taking into account many other components that are involved in the pathogenesis of systemic sclerosis, such as the epithelium, blood-derived cells, and other processes that are relevant to wound healing.[59] The events that underlie susceptibility to systemic sclerosis probably include both genetic and environmental factors. The main features of early systemic sclerosis are microvascular dysfunction and autoimmune phenomena.[60,61] Key factors that govern the amplification and progression of systemic sclerosis are also likely to be complex and multifactorial. This complexity is likely to underpin the diversity and clinical heterogeneity of systemic sclerosis. Finally, recognition that the capacity for resolution or regression of fibrosis and other manifestations of the disease is variable provides insight into long-term outcome.[62] Understanding the pathophysiology of systemic sclerosis has been important in an era of therapeutic progress, with development of more targeted biological and pharmacological approaches. Although falling well short of a definitive understanding of the processes that

underlie systemic sclerosis, current preclinical models of systemic sclerosis have permitted logical candidates to be selected for early-stage and proof-of-concept or proof-of-mechanism clinical trials.[63] Recognition of the association between systemic sclerosis and malignancy has strengthened the concept that autoimmunity might be central to the initiation or progression of the disease.[64,65] Notably, the forms of systemic sclerosis that are most associated with malignancy are often severe and express one of the specific hallmark ANAs of systemic sclerosis, anti-RNA polymerase III antibodies.[66,67]

Management

Baseline assessment and initial diagnostic investigations

The cornerstone of management of systemic sclerosis in the modern era is systematic baseline assessment and follow-up as specified by expert guidance that includes evidence levels where available.[68] The appendix summarises red flags for the development of specific, important complications of systemic sclerosis. Notably, overall outcome and survival appear to have improved during the past four decades,[69] which can be attributed to a more proactive approach to follow-up and improved recognition of organ-based complications that might be life threatening. Initial management plans need to consider the classification of systemic sclerosis, disease duration, the presence of any overlapping features of connective tissue disease that might need specific intervention, and recently updated EULAR and EULAR Scleroderma Trials and Research (EUSTAR) recommendations for management of scleroderma,[70] which include the level of evidence and the grade of recommendation. Additionally, the results of the baseline evaluation are used to determine the presence and severity of any organ-based complications.

Long-term organ-specific management, follow-up, and outcomes

Most organ involvement occurs early in the disease.[6] Although no disease-modifying drugs for systemic sclerosis exist, early screening and management of patients appears to improve mortality. Figure 3 shows our recommended algorithm for regular screening of organ involvement to detect early disease. Generally, regular pulmonary function testing is recommended during the first 3–5 years after diagnosis, since interstitial lung disease is an early complication of systemic sclerosis.[13,72] Patients, especially those with anti-RNA polymerase III antibody positivity, are counselled about the risk of scleroderma renal crisis and are advised to do regular home-blood-pressure monitoring.[73] Additionally, investigation for a possible associated malignancy might be appropriate for any case raising clinical suspicion. Routine screening of all patients is not recommended. Some of the major complications of systemic sclerosis are digital vasculopathy, gastrointestinal complications, lung fibrosis, pulmonary hypertension, cardiac fibrosis, scleroderma renal crisis, digital contractures, calcinosis, and acro-osteolysis (figure 4). Treatments for these major complications are diverse (figure 5).

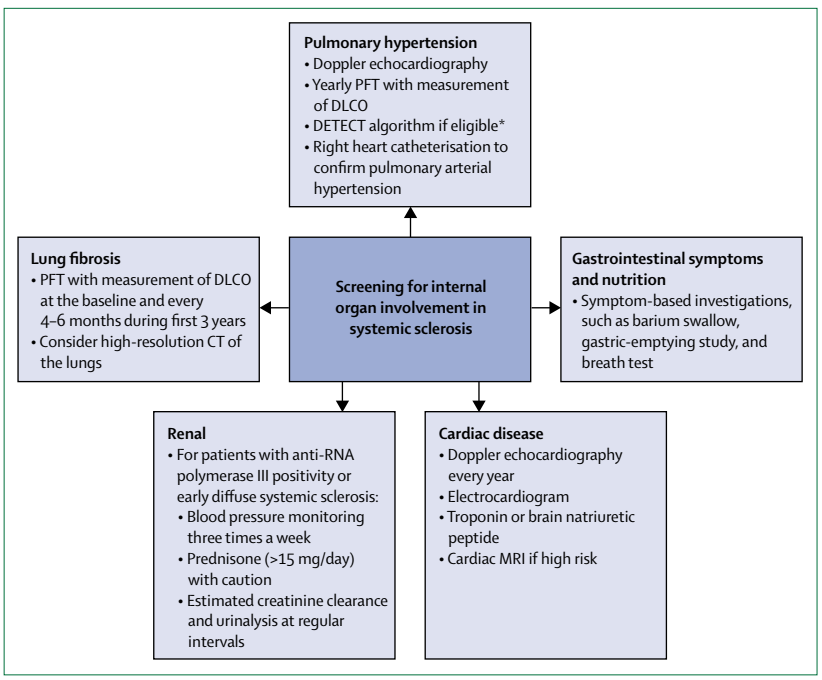

Figure 3: **Investigation strategy for systemic sclerosis**
Systematic investigation of newly diagnosed cases of systemic sclerosis and during regular follow-up is important to identify complications that might require management. This systematic approach allows proactive management and has been associated with improved overall survival in cohorts of patients with systemic sclerosis.[1] *The DETECT algorithm incorporates clinical and laboratory tests, PFTs, and transthoracic echocardiography for early detection of pulmonary arterial hypertension.[71] PFT=pulmonary function test. DLCO=diffusing capacity for carbon monoxide.

See Online for appendix

Skin and musculoskeletal disease—assessment and treatment

The skin is almost always involved in systemic sclerosis, except for patients with sine scleroderma. Although skin involvement can cause substantial morbidity (pruritus, depigmentation, open ulcers), it is not associated with increased mortality per se.[75,76] However, substantial skin involvement or rapid progressive skin involvement early in disease is associated with increased mortality and prevalence of internal organ involvement.[22] Generally, skin thickness tends to increase in early diffuse cutaneous systemic sclerosis and decrease in late diffuse cutaneous systemic sclerosis, although the time of peak skin involvement is typically 12–18 months after the onset of skin thickening. The duration of each phase might differ in each patient and the phases often overlap each other.[77] Studies from the EUSTAR database[78] have identified factors associated with an increased risk of skin worsening during follow-up.

Management of skin-associated complications consists of immune-modulating therapies. Clinical trials[79–82] have supported clinical benefits for methotrexate (15–25 mg/week) or mycophenolate mofetil (up to

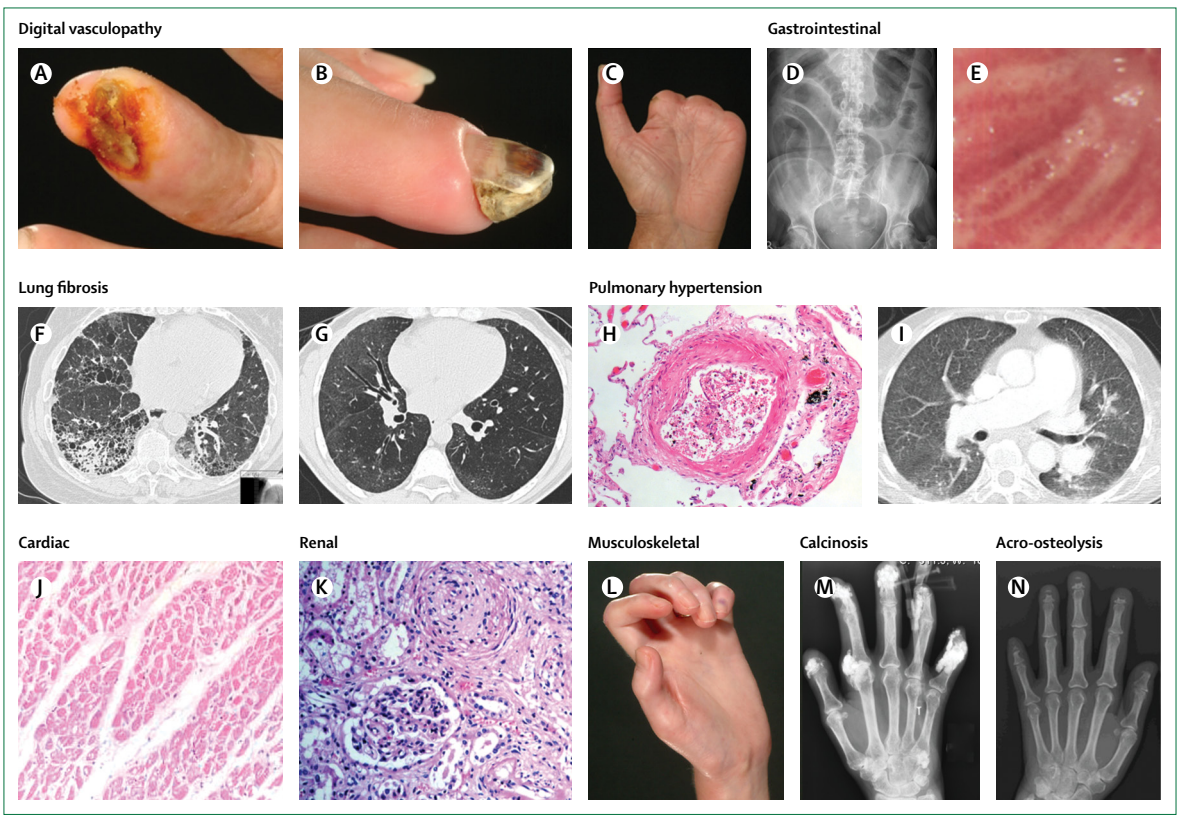

Figure 4: **Overview of major complications of systemic sclerosis**
Clinical and pathological or radiological features of the key organ-based complications of systemic sclerosis. Digital vasculopathy can lead to ulceration, gangrene, and amputation in severe cases. Lung fibrosis might have a usual interstitial pneumonia pattern or, more often, a non-specific interstitial pneumonia pattern. Pulmonary hypertension might be identified by enlargement of the pulmonary arterial trunk relative to the aorta and, if lung fibrosis is absent, is more likely to reflect pulmonary arterial hypertension. (A) Digital ulceration. (B) Dry gangrene. (C) Autoamputation. (D) Intestinal pseudo-obstruction. (E) Gastric antral vascular ectasia. (F) Lung fibrosis with a usual interstitial pneumonia appearance on high-resolution chest CT. (G) Lung fibrosis with an non-specific interstitial pneumonia appearance on high-resolution chest CT. (H) Pulmonary arterial hypertension shown histologically. (I) Pulmonary arterial hypertension shown on CT. (J) Cardiac fibrosis. (K) Scleroderma renal crisis. (L) Digital contractures. (M) Calcinosis. (N) Acro-osteolysis.

3 g/day). For more severe skin involvement, a post-hoc analysis by the Scleroderma Lung Study-I[83] supports daily oral administration of cyclophosphamide (up to 2 mg/kg per day). Pigment changes in skin, including increased skin tone and post-inflammatory hypopigmentation (salt-and-pepper appearance), can be distressing for patients. Pigment changes might be a serious cosmetic issue and existing treatments are scarce.

Musculoskeletal involvement can be an important and overlooked complication because of focus on internal organ complications. Key manifestations include arthralgia, inflammatory polyarthritis (rheumatoid arthritis-like disease), tendon friction rubs, subcutaneous calcinosis, and small and large joint contractures.[84] Treatment of musculoskeletal pain and function with systematic and intensive physiotherapy or occupational therapy and regular exercise programmes is important; non-steroidal anti-inflammatory drugs and low-dose daily prednisolone (less than 10–15 mg/day) might also be useful.

Intensive immunosuppression with haemopoietic autologous stem-cell transplantation (HSCT) rescue therapy has a substantial benefit in some patients with systemic sclerosis, especially in those with a poor prognosis and lung fibrosis.[85] Two controlled trials[86,87] have supported the use of autologous HSCT for the treatment of systemic sclerosis, with a better outcome than intravenous cyclophosphamide therapy over 12 months, although these studies also highlighted potential mortality (mostly due to severe cardiac disease) associated with this approach, which might preclude its use in cases that would otherwise benefit.[88] A multicentre randomised trial (SCOT study)[89] in the USA showed reduced treatment-related mortality for HSCT with selection of appropriate patients and experienced centres, thus confirming the feasibility of this approach in selected cases with a poor prognosis. Patient selection is crucial, and HSCT should be considered in patients with underlying interstitial lung disease or involvement of other internal organs and who have not improved or have worsened with conventional immunosuppressive agents.

Lung fibrosis

Lung fibrosis or interstitial lung disease is present in 80% of patients with systemic sclerosis, but only 25–30%

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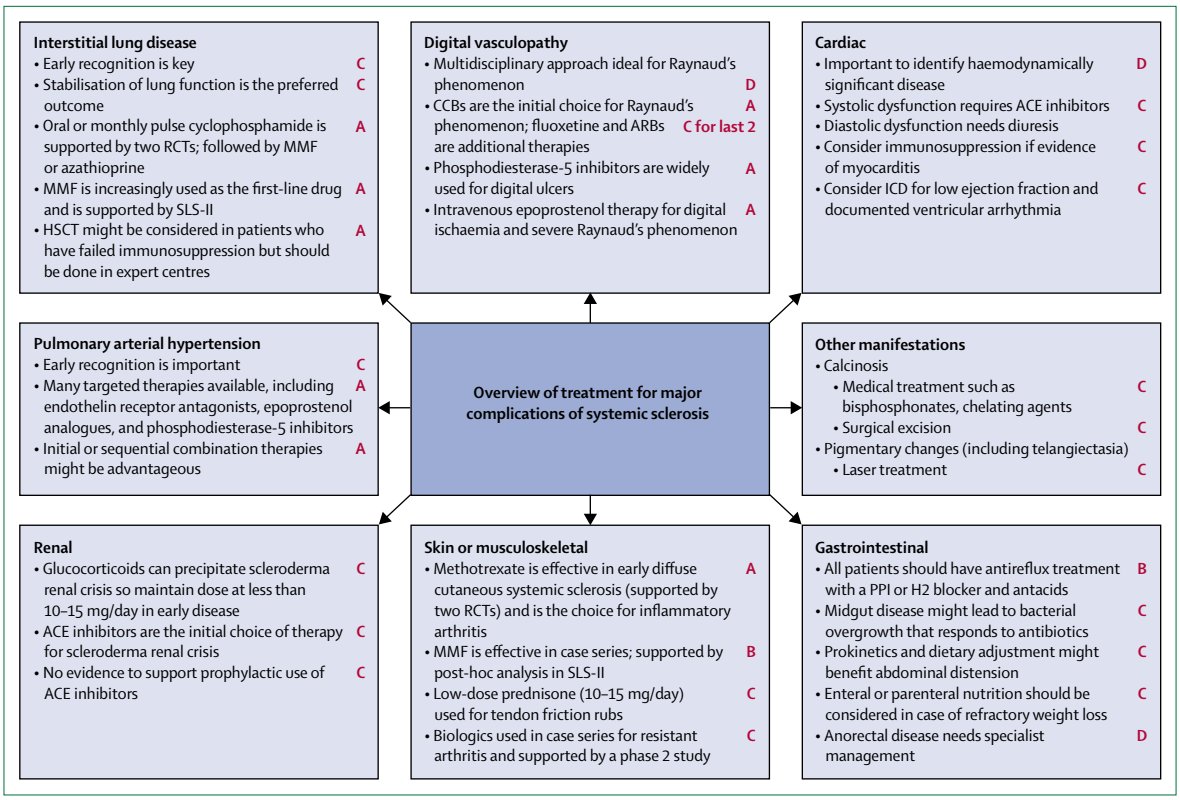

***Figure 5*: Treatment synopsis for major complications**
Summary of the key aspects of treatment for individual complications of systemic sclerosis, as informed by authors' opinions and the updated EULAR recommendations in 2017.[70] The strengths of recommendations (where A is the highest level of evidence and D is based on expert opinion) are provided based on the 2014 update of the EULAR standardised operating procedures for EULAR-endorsed recommendations.[74] EULAR=European League Against Rheumatism. RCT=randomised controlled trial. MMF=mycophenolate mofetil. sGC=soluble guanylate cyclase. CCBs=calcium channel blockers. ARB=angiotensin receptor blockers. ACE=angiotensin converting enzyme. SLS-II=Scleroderma Lung Study-II. HSCT=haemopoietic stem-cell transplantation. ICD=implantable cardioverter defibrillator. PPI=proton pump inhibitor.

develop progressive interstitial lung disease.[90] Interstitial lung disease is an early complication, with most patients developing severe restrictive lung disease in the first 5 years after the onset of symptoms. Interstitial lung disease generally stabilises during the first 4–6 years after the onset of scleroderma, highlighting the need for early and aggressive screening. Use of spirometry is not sensitive nor specific enough for determining early interstitial lung disease and high-resolution CT is needed to confirm the diagnosis.[91–95] Most patients have fibrotic non-specific interstitial pneumonitis and a lung biopsy is generally not done. High-resolution chest CT is not required on an annual basis and is generally only repeated to assess for progressive interstitial lung disease if there is a substantial decline in spirometry with measurement of gas transfer (diffusing capacity for carbon monoxide [DLCO]). Large clinical trials[96,97] have supported the use of daily oral or monthly pulse cyclophosphamide or daily oral mycophenolate mofetil for treatment of interstitial lung disease. Although the trials did not assess the appropriate duration of immunosuppressive therapy, we recommend at least 4–5 years of stable spirometry before careful tapering of medication.[98] Use of HSCT is supported for moderate and progressive interstitial lung disease; 85% of patients who were considered for HSCT had interstitial lung disease in the ASTIS study,[87] and 93% had underlying interstitial lung disease in the SCOT study.[89] These results also highlight that not every patient with interstitial lung disease requires immunosuppressive treatment, especially those with late systemic sclerosis. Clinical trials[98] have explored the potential of using drugs licensed for idiopathic pulmonary fibrosis, such as nintedanib or pirfenidone, for the treatment of interstitial lung disease. Rituximab has shown promise as a rescue therapy in some cases and is under trial.[99]

Pulmonary hypertension

Pulmonary arterial hypertension affects about 15% of patients with systemic sclerosis.[6] Unlike involvement of other internal organs, which is generally more common and severe in the diffuse subset, pulmonary arterial hypertension occurs more commonly in patients with limited cutaneous systemic sclerosis. Once a potentially lethal complication, early screening and detection have improved the outcome of pulmonary arterial

hypertension.[100] Although transthoracic echocardiography is done to screen for pulmonary hypertension, tricuspid regurgitation can be absent in about 15–20% of patients and pulmonary arterial hypertension can be missed in up to 30% of cases.[101] An algorithm included in recommendations at a consensus meeting[102] incorporates clinical, laboratory, and pulmonary function tests and transthoracic echocardiography for early detection of pulmonary arterial hypertension.[71] However, it is important to recognise risk factors in clinical practice, such as decreased DLCO, increased ratio of forced vital capacity to DLCO, the presence of anti-centromere antibodies, ANA pattern, and increased disease duration. The gold standard for diagnosis is right heart catheterisation, which can differentiate pulmonary arterial hypertension from other causes of pulmonary hypertension (such as systolic or diastolic dysfunction).

For the **algorithm** see http://detect-pah.com/

Figure 5 shows the multiple approved therapies for management of pulmonary arterial hypertension.[103,104] Clear differences in outcomes for pulmonary arterial hypertension are emerging between different associated connective tissue diseases; pulmonary arterial hypertension associated with systemic sclerosis has a worse outcome than pulmonary arterial hypertension associated with mixed connective tissue disease or systemic lupus erythematosus.[100] Borderline cases of mean pulmonary artery pressure elevation in patients with systemic sclerosis are identified from screening programmes,[105] and these patients are at high risk of developing pulmonary arterial hypertension.[106] Treatment of pulmonary hypertension in systemic sclerosis is similar to other forms of this complication; it builds on an emerging evidence base and follows consensus recommendations that have recently been updated.[107] Data from long-term trials[108–110] that include patients with systemic sclerosis-associated pulmonary arterial hypertension confirm benefit for targeted therapy on morbidity and mortality. Importantly, it appears that as more intensive treatments (eg, combination therapy) are used, their relative benefit on systemic sclerosis-associated pulmonary arterial hypertension is similar to other forms of pulmonary arterial hypertension.[108–110]

Gastrointestinal manifestations

Gastrointestinal tract involvement in systemic sclerosis is almost universal but varies in severity and clinical effect.[111] Upper gastrointestinal tract involvement is a common clinical feature of systemic sclerosis.[30] Any area of the gastrointestinal tract can be affected, although the upper and lower tracts are most frequently affected.[111] Involvement of the gastrointestinal tract leads to reflux, bloating, distension, constipation, diarrhoea, and anorectal incontinence. The patterns of gastrointestinal disease can be most usefully defined by the symptoms that develop, and this allows systematic investigation and treatment.[112,113] Gastric antral vascular ectasia (so-called watermelon stomach) is an important and increasingly recognised manifestation of the gastrointestinal tract that requires specific investigation and treatment.[111] Gastric antral vascular ectasia can cause silent anaemia, which often presents with extreme fatigue and weakness and has been associated with anti-RNA polymerase III autoantibodies in some studies.[111] A well established consensus for management of gastrointestinal disease that focuses on the problems and symptoms rather than on the anatomical site now exists.[114] The existence of this consensus is advantageous since many features, such as bloating and distension, might arise from various systemic sclerosis-related mechanisms. These recommendations[115] provide a guide to management of secondary care and referral to specialist units. Although vasculopathy and fibrosis are generally considered the key pathological drivers in gastroinstestinal disease, studies[115,116] suggest that immunomodulatory strategies might be beneficial in some cases, although gastrointestinal disease is generally not considered a manifestation of an immune-responsive disease. Weight loss and malnutrition are important manifestations that might severely affect function and quality of life and lead to substantial comorbidity.[117] Monitoring of these manifestations is important,[118] and enteral or parenteral feeding supplementation might be beneficial.[119] However, enteral supplementation should be used with caution because of the risks of aspiration.

Scleroderma renal crisis

Scleroderma renal crisis is defined by the development of thrombotic microangiopathy, with accelerated-phase hypertension and progressive acute kidney injury. Criteria for the diagnosis and management of scleroderma renal crisis have been suggested,[73] but it is important in clinical practice to consider whether any other treatable renal disease is present, especially if clinical or serological features of overlapping syndromes, including systemic lupus erythematosus or vasculitis, are observed. Some cases of scleroderma renal crisis are normotensive, and these cases have a particularly poor outcome. The explanation for this poor outcome is unclear, although one possibility is that these patients have a poor left-ventricle function, making it difficult to mount a hypertensive response to the high afterload.[34,120] The mainstay of management of scleroderma renal crisis is immediate initiation of angiotensin converting enzyme (ACE) inhibitors following a definite diagnosis.[121] Other supportive measures are crucial.

The presence of pulmonary oedema or other organ-based complications of hypertension might reflect systemic vascular endothelial perturbation associated with systemic sclerosis rather than other causes of accelerated-phase hypertension. Management of scleroderma renal crisis is best done in concert with renal and intensive-care experts and according to consensus recommendations.[73] Several markers have been shown to reflect outcome, including ACE inhibitors[122] and substantially elevated N-terminal pro b-type natriuretic peptide (NT-proBNP) concentrations.[123] Positivity for anti-RNA polymerase III

antibody is predictive of scleroderma renal crisis: about 25% of positive cases develop scleroderma renal crisis. The frequency of scleroderma renal crisis appears to be decreasing, although this might reflect an increased number of systemic sclerosis cases being identified with a reduced risk, comprising the limited cutaneous systemic sclerosis subset.[124] It has been suggested that targeting complement activation might benefit some patients with scleroderma renal crisis.[125] Use of ACE inhibitors in prevention is highly debated, although studies[122] have suggested a worse outcome for scleroderma renal crisis after treatment with ACE inhibitors. Since around half of the patients with scleroderma renal crisis who require dialysis need ACE inhibitors for long-term renal support, and because these patients have a high mortality, it is appropriate to consider ACE inhibitors for renal transplantation. However, this decision should be delayed for 18–24 months to be certain that spontaneous recovery of adequate renal function does not occur.

Cardiac disease

The frequency of cardiac involvement in systemic sclerosis is probably underestimated.[126] Patients might present with sudden and severe cardiac disease that was not previously recognised. Occult cardiac involvement almost certainly contributes to sudden death in patients with systemic sclerosis and is often associated with undercurrent sepsis.[127] A multifaceted approach to investigation is essential and is augmented by cardiac MRI, although even this approach can be limited and requires expert interpretation. Late gadolinium enhancement is a hallmark feature that can confirm focal or diffuse cardiac fibrosis, but less obvious intrafascicular fibrosis might not be detected. Likewise, inflammatory features and improved functional and structural assessment of cardiac systemic sclerosis is improving our understanding of this important and lethal manifestation.[128] Assessment for placement of an implantable cardioverter defibrillator is important, and criteria for cases of systemic sclerosis should be different from those for other forms of cardiac abnormality. Loop-recording devices might reveal infrequent arrhythmias. These tools[129] might help to define those patients at risk of sudden severe arrhythmia who might benefit from an implantable cardioverter defibrillator. As well as occult disease and the challenge of interpreting the clinical importance of minor electrophysiological imaging abnormalities, a particularly important aspect of cardiac systemic sclerosis is reduction in cardiac reserve and function, which makes management of intercurrent sepsis, hypertension, or pulmonary vascular disease challenging.[130]

Other non-lethal manifestations of scleroderma

Other non-lethal manifestations of scleroderma include Raynaud's phenomenon; calcinosis; fatigue; musculoskeletal and other chronic pain syndromes; sexual dysfunction; and emotional, psychological, and financial burden. It is important to focus on these non-lethal manifestations, together with the associated complications and effect on quality of life and function, because these manifestations are often of more concern to a patient with newly diagnosed or established systemic sclerosis than is the risk of life-threatening complications that might be the medical priority. Additionally, there are other less-recognised manifestations that can be a major burden. These manifestations include facial changes and oral complications such as sicca symptoms, dental disease, and limited jaw opening, and they might be amenable to treatment and require specialist education and advice.[131]

The problem of digital ulcers is increasingly recognised.[132] Digital ulcers occur in around half of systemic sclerosis cases during their disease history, and about one in five patients might have this complication at any one time.[133–135] There is now a better appreciation of the effects of digital ulcers, which include impaired function, pain, and loss of employment, as well as the more obvious medical complications of cellulitis, osteomyelitis, digital infarction, and severe pain.[134] Drugs have been licensed for the prevention of digital ulcers in some European countries, and there is a consensus by experts that systemic treatments are valuable.[24] Treatment of digital ulcers with drugs or systemic therapies needs to be combined with appropriate expert local care and dressings, and this treatment usually benefits from specialist nurse input. Case stratification has been defined,[136,137] allowing digital ulcers to be categorised with other manifestations of systemic sclerosis into milder or more severe disease, which assists in appropriate management. Evidence-based treatments include phosphodiesterase-5 inhibitors and endothelin receptor antagonists, although some studies have not shown a clear treatment benefit.[138,139]

Calcinosis remains a challenging non-lethal complication, although understanding of its pathogenesis and assessment is being advanced through collaborative studies.[140–142] Numerous medical therapies were found to be effective in case series,[143] but there is a scarcity of convincing data to recommend these therapies for the management of calcinosis. Similar to other forms of calcific tissue damage, sodium thiosulphate has been used systemically and topically to treat calcinosis, although the results have been mixed, with no clear sign of benefit.[144] In the absence of robust medical therapy, excision of the underlying calcinosis by an experienced surgeon provides the best opportunity for debulking of calcific deposits.

Evolution of management strategies

Autoantibodies in disease classification

Autoantibody profiles in systemic sclerosis are important for diagnosis, and hallmark ANA patterns are now part of the classification criteria for systemic sclerosis.[15] However, there is a broad range of systemic sclerosis-specific antibodies and these are associated with specific internal organ complications.[145] Because the ANA

patterns are generally mutually exclusive, this allows patients to be stratified early in their natural history and helps provide the basis for a stratified approach to management. Autoantibodies in systemic sclerosis include anti-centromere (associated with limited systemic sclerosis and pulmonary arterial hypertension), anti-Scl-70 (associated with diffuse systemic sclerosis, progressive lung fibrosis, digital ulcers, and hand disability), and anti-RNA polymerase III (associated with diffuse systemic sclerosis, scleroderma renal crisis, and hand disability). Additionally, a nucleolar pattern of ANAs is associated with progressive interstitial lung disease and pulmonary arterial hypertension.[146] These antibodies can aid prognostication and direct early screening for disease.[147] Some cases are ANA negative and generally have a distinct subtype, which can be associated with a poor outcome.[148] Other cases are predictive of features of overlap scleroderma.[149]

Molecular classification

There is an interest in developing better ways to classify systemic sclerosis, and one approach that has proven fruitful is the definition of gene expression profiles of the skin.[150] This definition has permitted classification of diffuse cutaneous systemic sclerosis into several subsets, and emerging data suggest that similar subgroup classification can be done for limited cutaneous systemic sclerosis.[151] This subgroup classification is important because subsets based on intrinsic gene expression appear to be independent of skin involvement and represent an inherent property of the patients.[152] Thus, these subsets might relate to genetic susceptibility and are providing exciting insight into classification and pathogenesis.[61]

Stratified and precision medicine

A more formal stratified approach to management of systemic sclerosis is needed, since systemic sclerosis is a heterogeneous disease with varied outcome and different patterns of organ-based complications. The ability to subgroup cases based on ANA pattern, clinical subset, and other specific molecular characteristics of skin biopsies is powerful.[151] Alongside molecular-based subgrouping is the integrative approach of combining clinical and laboratory tests and molecular features, which has been effective in stratifying specific complications of systemic sclerosis, such as pulmonary arterial hypertension, by risk. Thus, a stratified approach is very tractable and an individualised precision medicine strategy, such as a strategy based on potential serum genetic markers,[152–154] might also be useful and possible in the future and is an active area of research. New and improved molecular surrogates are emerging and might develop into validated biomarkers. Interleukin 6 has been implicated as a potential biomarker of a poor outcome for skin[155] or lung[156] fibrosis, especially in patients with mild lung fibrosis, and this is interesting in view of the reported potential benefit for targeting the interleukin 6 receptor in systemic sclerosis.[155]

Translational studies

Systemic sclerosis is an unmet medical need and an orphan indication. Therefore, systemic sclerosis lends itself to innovative drug development, and this, coupled with an increasing understanding of its pathogenesis, has made systemic sclerosis a suitable disease for experimental medicine studies and translation.[157] Thus, the added value and potential of therapeutic progress in systemic sclerosis with research translation are substantial. Forward translation can be supported by improved and more defined mouse or other animal models of systemic sclerosis. Additionally, systemic sclerosis offers the opportunity for direct access to lesional skin tissue, and explanted fibroblasts have been extensively studied.[158,159] However, mouse and other preclinical models of systemic sclerosis can only reflect part of the disease and need to be tailored to the interventions being assessed. In particular, as with mouse models of other diseases, many interventions seem to attenuate some of the simple models of systemic sclerosis, such as bleomycin-induced models of skin or lung fibrosis.[160] Biomarkers have been developed and validated that might reflect skin disease.[161,162] Moreover, other modern molecular approaches are being applied to integrate data in a way that might increase understanding of potential biomarkers, targets for therapy, or key pathogenic mediators or pathways by integrating these with potential treatment responses to medication.[158,163,164]

Future outlook

Some controversies and uncertainties exist regarding the management of early disease and duration of treatment for systemic sclerosis. Unlike rheumatoid arthritis, for which it is universally accepted that immunosuppressive treatment might be required life long, the duration of immunosuppressive treatment for progressive skin fibrosis and interstitial lung disease (two of the most common organ involvements for immunosuppressive treatment) is unclear. Whether ACE inhibitors should be used for prevention of scleroderma renal crisis, especially in patients with early diffuse cutaneous systemic sclerosis or anti-RNA polymerase III antibody positivity, is highly debated, although presently this is not recommended. The optimum way to assess disease activity remains uncertain and new composite indices are being developed;[162] a similar approach has been used in clinical trials[164,165] to develop composite measures that could reflect damage or severity of systemic sclerosis. These developments might underpin future clinical trial design and success.

Conclusion

Systemic sclerosis remains a major medical challenge, although its pathogenesis is slowly being elucidated and overall survival and treatment opportunities are improving. A more complete understanding of the clinical features, heterogeneity, and interplay with other related medical conditions has been attained. Treatment options for some of the organ-based complications are

substantially improved and, for manifestations such as pulmonary arterial hypertension, there is optimism around the use of combined approaches and intensive treatment. Improved classification and understanding of key pathogenic drivers will allow a move to better combination and disease-modifying therapies. In this way, we anticipate that assessment and treatment of systemic sclerosis will continue to advance and that some of the lessons learned might also benefit other immune-mediated or fibrotic diseases, including more common diseases of medical importance and clinical effect.

Contributors

CPD and DK jointly conceived, drafted, and wrote this article. The text has been critically revised by both authors who have also approved the final submitted version.

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