Review

Current management strategies for systemic sclerosis

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ABSTRACT

Systemic sclerosis remains a challenging disease despite progress that has taken place in the management of organ-based complications. Overall management strategies need to take into account the features of the disease that are common to almost all patients such as skin involvement, gastro-oesophageal manifestations and secondary Raynaud's, as well as identify less frequent but critical manifestations that impact on survival including heart, lung, renal and more severe GI involvement. Treatments can be considered to be disease-modifying or symptomatic. In addition, it is important to address more generic problems such as the emotional, psychological and economic impact of a chronic autoimmune rheumatic disease. This article reviews general approaches to disease assessment and management and relates this to subset and stage of the condition.

Although there are now published recommendations for management and a growing evidence base that underpins treatment of systemic sclerosis, it remains one of the most challenging of autoimmune rheumatic diseases. This results from the wide spectrum of clinical presentation, with varying degree of severity of skin involvement, digital vasculopathy and pattern of internal organ complications. In practice this makes the selection of management strategies challenging, and generally they are guided by the dominant clinical problem and potential development of complications in the future. Disease course can, to a degree, be predicted by the extent of skin involvement, serological features and potentially other disease characteristics, obtained from history, examination and clinical tests. This article summarises the clinical factors that determine treatment approaches and reviews current approaches to management of the major disease manifestations.

Clinical hetereogeneity and classification

A wide spectrum of disease characteristics of varying severity has made disease classification difficult. The task has been additionally complicated by the need of clear diagnostic criteria to distinguish between presence and absence of disease. Multiple attempts have been made to systematise clinical and serological features in order to define distinct disease sub-groups while at the same time authors have attempted to compile criteria to enable early diagnosis and identification of cases, even if they have very mild or non-existent skin involvement. Very recently published revised classification criteria for SSc represent a landmark for research and clinical practice. These were developed by a large group of experts under the auspices of ACR and EULAR (1, 2) using a Delphi technique. The new criteria include 9 items, are applicable to the whole disease spectrum and reflect features that result from all three pathogenetic aspects of the condition – vasculopathy, autoimmunity and fibrosis. Those include skin thickening, fingertip lesions, telangiectasia, abnormal nailfold capillaries, Raynaud's phenomenon, SSc-specific autoantibodies and presence of pulmonary complications (PH or PF) (3).

There is a lack of agreement in the scleroderma field about the sub-classification of SSc. In the majority of cases authors define SSc subsets on the basis of skin disease extent, although capillaroscopic and serological findings as well as organ complications have also been included. Several classifications of the disease have been proposed, including subdivision into four groups – SSc sine scleroderma (no skin involvement), limited (skin tightness distal to metacarpophalangeal joints), intermediate (skin tightness affecting whole arm, but no truncal involvement) and

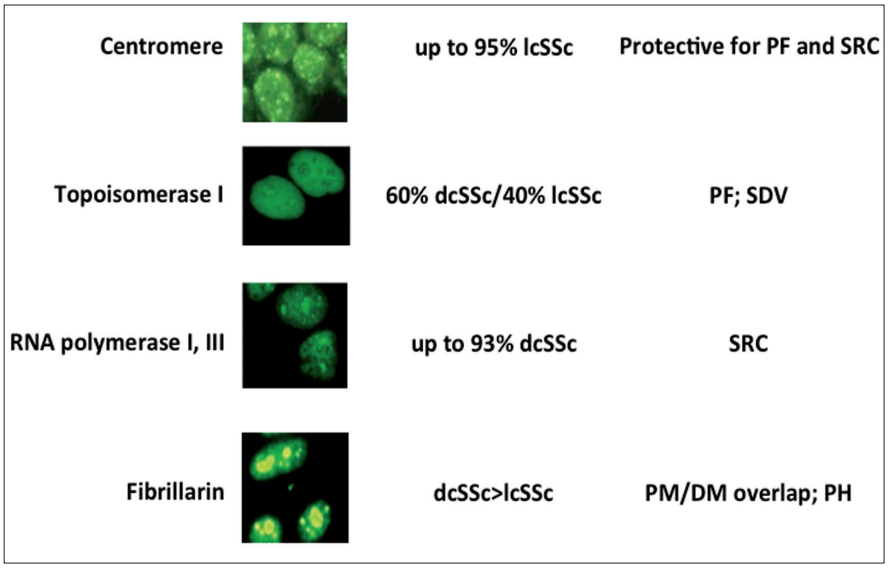

Fig. 1. Autoantibodies in risk stratification of systemic sclerosis.
Almost all patients with systemic sclerosis have positive ANA and this is usually one of the hallmark SSc associated reactivities. However these are mutually exclusive and so association studies identify cases at increased or reduced risk of important complications.
The common associations for the four commonest SSc-specific ANA patterns are shown together with typical pattern of staining by immunofluorescence on Hep-2 substrate at 1:100 dilution of serum.

diffuse (skin tightness involving both extremities and trunk) (4) or six subgroups: I – Diffuse; II – Intermediate (distal to elbows/knees, but proximal to metacarpophalangeal joints); III – Digital (sclerodactyly only); IV - SSc sine scleroderma; V – undifferentiated CTD with some SSc features and VI – CREST (5). Most current publications use the sub-division of SSc into limited cutaneous (lcSSc), where only skin distal to elbows and knees is involved and diffuse cutaneous subset (dcSSc), where both areas distal and proximal to the elbows and knees are affected (6). Multiple independent studies report that degree of skin involvement is associated with survival with patients with higher peak modified Rodnan skin score (mRss) having higher mortality (7-9). On the other hand, it is still unclear if subdividing SSc cases into 3 or more groups that show progressively worse survival with the increase of skin involvement extent contributes to the better understanding of the disease (10). Throughout the current review paper we have used the classification of disease into diffuse and limited cutaneous subset, based on the presence or absence of skin tightness proximal to the elbows and knees (6).

Auto-antibodies and disease subset

DcSSc is associated in general with higher incidence of organ complications and worse survival (8, 9), although all SSc-associated complications can be observed in both disease subsets. Although patients with lcSSc are at a lower risk of organ disease, a substantial proportion of them can develop organ complications, which warrants continuous clinical monitoring and regular internal organ tests. Even though skin tightness improves in about 80% of cases with dcSSc (9) and can be negligible in lcSSc cases, there is still risk of organ involvement development in patients with mild skin disea se and the relationship between skin involvement and morbidity and mortality is complex (9, 11, 12).
Autoantibody testing is an important part of initial assessment in patients with possible diagnosis of SSc and serological profile is used for both diagnosis and risk prediction in SSc cases. Autoantibody specificities do not change over time and although serum levels of autoantibodies vary within and between patients and even can become undetectable (13-15), they have no clear relationship with disease activity and severity and repeat measurement has no utility in clinical practice. The three most common, highly scleroderma-specific autoantibodies – anti-centromere antibody (ACA), anti-topoisomerase I antibody (ATA) and anti-RNA polymerase antibody (ARA), have very strong associations with disease presentation and pattern of internal organ complications (Fig. 1).
ACA are found almost exclusively in lcSSc cases - 93-95% of all ACA positive patients (16-18) and have strong negative association with SSc-associated pulmonary fibrosis (PF) and scleroderma renal crisis (SRC) (17-21), while its perceived association with pulmonary hypertension (PH) is yet to be confirmed in studies of right heart catheter diagnosed PH in unselected SSc cases. ATA can be found in both lcSSc and dcSSc patients and patients positive for ATA are at an increased risk of interstitial lung disease and digital vasculopathy-related complications (17-19). The majority of ARA positive patients (67–93%) develop dcSSc (22-24) and are at a significantly increased risk of SRC with just under half (up to 43%) of ARA positive subjects developing SRC (22, 25). Other scleroderma-specific autoantibodies, including anti-U3RNP antibodies, anti-Th/To antibodies and anti-U11/U12 antibodies are much rarer. Anti-U3RNP predicts severe disease and poor prognosis in black patients and correlates with increased risk of PH development (26, 27) while anti-U11/U12 antibody is associated with high risk of PF (28). Anti-Th/To antibody is associated with the limited cutaneous subset and increased risk of PH (29).

Current treatment approaches

Due to the complexity of SSc and the wide spectrum of disease with substantial variety in pattern of organ involvement, treatment approach is tailored according to each patent's needs and taking into account disease subset, stage and organ-based complications (Fig. 2). As the pathogenic mechanisms underlying SSc become better defined through greater understanding of the pathobiology of the disease there has been increasing focus on the potential development of targeted therapies that may attenuate key pathways or media-

tors, drawing analogy with progress in other autoimmune rheumatic diseases (30). Immunosuppressive treatments remain of key importance for treatment of diffuse skin involvement and organ complications in SSc patients, although there is a range of other supportive therapies that are essential for the management of this complex condition.

Immunosuppressive and anti-fibrotic therapies

The various currently used immunosuppressive medications for scleroderma skin and organ-based disease address mainly two aspects of SSc pathogenesis – inflammation and fibrosis. It is often difficult to distinguish potential immunological or anti-inflammatory mechanisms from anti-fibrotic strategies because of the complex underlying biological processes.

– Cyclophosphamide (CYC)

CYC is the only immunosuppressive agent that has been shown to benefit SSc-associated PF and skin disease in two randomized, double-blind, placebo-controlled trials – the Scleroderma Lung Study (SLS) (31) and the FAST trial (32). Although both trials showed statistically significant differences in FVC between the active and placebo groups after 12 months of treatment, the differences were small and not clinically significant. Only the SLS study recorded skin score in the study subjects and showed significant difference between the two groups favouring the active treatment, although the effect was not sustained after treatment discontinuation.

– Mycophenolate mofetil (MMF)

No controlled, prospective data are available to support the use of MMF in SSc patients, although retrospective cohort analyses and prospective open-label studies have suggested it may benefit skin disease and PF (33-36). Currently there is an on-going trial comparing the use of MMF and oral CYC for the treatment of PF (Scleroderma Lung Study II).

– Methotrexate (MTX)

Two prospective, controlled trials investigated the use MTX in SSc. Both demonstrated only trend towards significance in improvement of mRss among the actively treated patients compared to those on placebo (37, 38). As MTX is an established therapy for inflammatory arthritis and polymyositis/dermatomyositis, it is generally preferred for the management of SSc overlap syndromes.

– High dose immunosuppression with autologous haematopoietic stem cell transplantation (HSCT)

The results of two prospective controlled trials of high dose immunosuppression followed by HSCT have been published to date – the American Scleroderma Stem Cell versus Immune Suppression Trial (ASSIST) (39) and the Autologous Stem cell Transplantation International Scleroderma (ASTIS) Trial (40). ASSIST recruited only 19 patients, who were randomised to receive HSCT or ivCYC and were followed up for 12 months. There were no deaths in either group for the duration of the trial and at 12 months there was improvement in both pulmonary function and skin tightness among the HSCT treated patients while there was none among the controls. The much larger ASTIS trial recruited 156 patients. Although at 2 years the HSCT group had a significantly greater improvement in skin score and vital capacity, HSCT was associated with 10% treatment-related mortality and at 2 years overall and event-free survival in both groups were very similar and comparable to survival in other published cohorts treated with conventional immunosuppression. This suggests

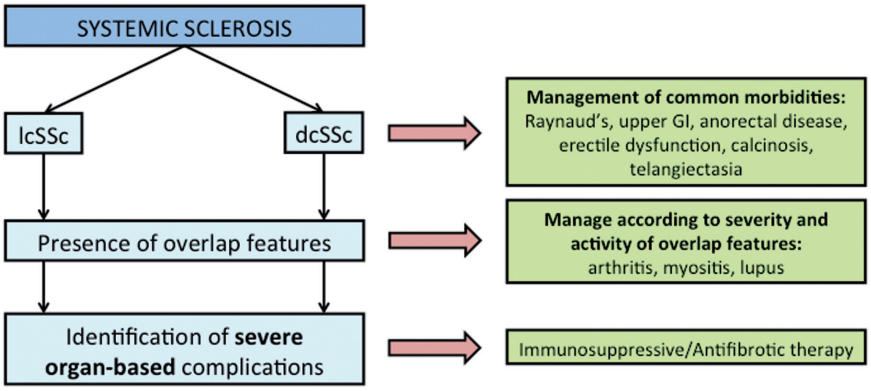

Fig. 2. Overview of current management of systemic sclerosis.
Almost all cases of systemic sclerosis can be classified by the extent of skin involvement into one of three categories – diffuse or limited disease. General treatment approaches are summarised. It is important to identify overlap features which can occur in up to 20% of cases and require different therapeutic approaches. Likewise a small number of cases have internal organ involvement without skin disease and these cases are generally managed in a similar way to those with limited subset, focusing on vascular symptoms and assessment or internal organ complications.

Table I. Immunosuppressive treatment for systemic sclerosis.

Systemic sclerosis complications		Immunosuppressive agents
Active skin involvement		Mycophenolate mofetil Methotrexate Cyclophosphamide Rituximab Intravenous immunoglobulin
Organ complications	Pulmonary fibrosis	Mycophenolate mofetil Cyclophosphamide Rituximab
	Cardiac scleroderma	Mycophenolate mofetil Cyclophosphamide
	Renal crisis	low dose MMF

that HSCT has a role in SSc treatment, although appropriate case selection is important, especially in the context of improving survival among SSc patients. Scleroderma Cyclophosphamide versus Transplant (SCOT) trial is another prospective controlled trial which is on-going.

– Imatinib

The promising preclinical studies and case reports on Imatinib use in SSc (41) led to three open-label clinical trials looking at improvement in skin fibrosis (42, 43) and pulmonary fibrosis (44) and two placebo-controlled trials (45, 46). Unfortunately in all there was significant proportion of patients developing adverse events, with fluid retention and GI disturbances being the most frequent. Although the open-label studies found statistically significant improvement in skin sclerosis and lung function compared to baseline (42, 44), no benefit for skin or lung was observed in the placebo-controlled trials (43, 45).

– Rituximab

Over the recent years, Rituximab has emerged as a potential treatment for SSc. Although it has not been tested in a controlled trial, several publications reporting case series and prospective open-label studies presented promising results, including improvement in lung function and skin score (47-51). Another study, reporting case series of SSc patients with severe and progressive ILD, who had not responded to treatment with other more commonly used immunosuppressants, demonstrated stabilisation and improvement in lung function in 7 out of the 8 patients after Rituximab (52).

– Intravenous immunoglobulin (ivIg)

Although several open-label studies, including patients with various disease duration from both subsets have showed that treatment with ivIg may benefit scleroderma skin disease (53-55), a prospective, double-blind, placebo-controlled study failed to show any difference in mRss change between patients treated with ivIg and placebo 12 weeks after randomisation (56). In an extension of the trial, non-respondents from both arms were retreated with ivIg and there was a significantly greater improvement in mRss at 60 months among those who had received active treatment twice, but the difference disappeared at the end of the study, suggesting that there may be some benefit from repeated administration of ivIg.

– Hyperimmune caprine serum and induction of tolerance to human type I collagen (CI)

There is evidence that relatively subtle immunomodulation using either orally administered bovine type I collagen or subcutaneous hyperimmune goat serum (AIMSPRO®) may benefit skin tightness in late SSc cases from prospective, placebo-controlled trials (57, 58).

– Role of glucocorticosteroids in the treatment of systemic sclerosis

Very few studies (only one randomised, controlled) report use of pulsed glucocorticosteroids (GCSs) alone in SSc and those suggest some benefit for ILD and skin (59-62). Nevertheless, high doses GCSs are known to associate with development of SRC (33, 63-65) and are therefore avoided, especially in subjects with early dcSSc. Although GCSs in low doses (≤15 mg/day prednisolone or equivalent) are often used in the management of SSc as an adjuvant therapy to immunosuppressive agents and have been described in multiple studies, no controlled data are available to support their effectiveness (66).

Treatment for skin disease

Treatment of skin sclerosis with DMARDs is indicated in patients with the diffuse subset of SSc, generally those in the first several years of disease, who have active skin involvement. The effect of various immunosuppressive and anti-fibrotic treatments has been reviewed in the previous section. Although most robust evidence for treatment effect is obtained from randomised, placebo-controlled trials, strict inclusion/exclusion criteria, small patient numbers and restricted trial duration often lead to inconclusive results. Observational studies offer an alternative, where larger numbers of patients can be followed for several years and may prove more appropriate when exploring drug effects in chronic and slowly-progressive diseases such as SSc. Unfortunately, the UK Scleroderma Observational Study (67) failed to demonstrate any difference in the effect of several standard treatment protocols on mRss after 3 years. The European Scleroderma Observational study (ESOS, http://www.ssc-esos.net/home.asp) is a larger study, which is ongoing. Often active skin inflammation is associated with significant pruritus, which can be responsive to low dose glucocorticosteroids, antihistamines or leukotriene receptor antagonists (montelukast). Telangiectasias are generally a cosmetic problem and when affecting the face, can be treated with laser therapy. Calcinosis can contribute greatly to hand disability and can become infected or lead to ulceration of the overlaying skin with discharge of calcium deposits. Even when surgically removed, it often recurs. Although there is some evidence that minocycline can be useful in treatment of calcinosis in lcSSc patients (68), an open-label trial of 31 SSc patients treated with minocycline, using subjects from the D-Penicillamine study as controls, did not show any statistically significant difference in the change in skin scores of both groups after 1 year of treatment, suggesting no benefit from minocycline treatment (69).

Raynaud's phenomenon therapies

Successful management of Raynaud's phenomenon requires some changes in patients' lifestyle, including wearing warm clothing and avoiding exposure to cold temperatures, as well as reducing consumption of caffeinated drinks and smoking. A number of vasodilators have been shown to benefit Raynaud's symptoms, including Ca channel blockers, angiotensin II receptor antagonists (but not angiotensin-converting enzyme inhibitors) and selective serotonin reuptake inhibitors (70-73). More advanced therapies, which are considered in patients with severe symptoms, unresponsive to conventional treatments, such as critical digital ischaemia or recurrent digital ulcers, include phosphodiesterase type 5 inhibitors, prostacyclin analogues and endothe-

lin receptor antagonists (74-77). There have also been developments in the formulations for nitrates used for topical application with similar efficacy, but less severe side effects (78). Surgical treatment with sympathectomy may be considered if other treatments fail.

Treatment for gastro-intestinal involvement

As a degree of oesophageal involvement can be found in the great majority of SSc patients, acid-reducing treatments, such as proton pump inhibitors and histamine H_2 receptor antagonists are prescribed in the majority of SSc patients. In addition, prokinetics are often needed to aid with symptoms of dysphagia. Small bowel involvement with development of bacterial overgrowth requires rotation antibiotics, although in milder cases, probiotic treatment can significantly alleviate symptoms of distension (79). In patients with malabsorption due to pancreatic insufficiency, enzyme replacement can be of help. Large bowel involvement with resulting constipation requires regular use of laxatives, while faecal incontinence may respond to surgery or nerve stimulation.

Pulmonary fibrosis treatment

PF can be present in a large proportion of patients with SSc, although only those with progressive extensive disease require immunosuppressive treatment (80. 81). In addition to the immunosuppressive therapies discussed in previous sections, N-acetylcysteine has been shown to improve outcome significantly when added to standard treatment with Azathioprine and oral steroids, compared to that treatment alone (82). In end-stage disease, lung transplantation can be considered.

Pulmonary hypertension treatment

General management of PH involves the use of diuretics, anticoagulation, Oxygen and Digoxin for the treatment of heart failure (83). The advanced therapies that have been demonstrated to benefit exercise performance include prostanoids (epoprostenol, treprostinil and iloprost), endothelin-1 receptor antagonists (bosentan and ambrisentan) and phosphodiesterase-5 inhibitors (sildenafil and tadalafil).

– Prostanoid therapy

Three agents have been licensed for treatment of PAH: epoprostenol, treprostinil and iloprost. The only agent shown to benefit SSc-associated PH is epoprostenol demonstrating favourable effect on 6-minutes walking distance (6MWD), haemodynamics, functional class and Borg dyspnoea score (84).

– Endothelin receptor antagonists

Bosentan is a dual endothelin-1 receptor antagonist licensed for use in patients with PAH. This is based on two trials (85, 86) showing improvement in 6MWT, cardiac haemodynamics, functional class and increase in time to clinical deterioration compared to placebo. Both studies included patients with iPAH and PAH associated with connective tissue disease (CTD-PAH) and subgroup analysis of the patients with CTD-PAH demonstrated stabilisation of exercise capacity and delayed disease progression, although the difference between the actively treated group and those on placebo showed only trend towards significance (87).

Ambrisentan is a selective endothelin-1 receptor antagonist. Two randomised, double-blind, placebo-controlled trials assessing safety and efficacy of three different doses of the drug against placebo showed increase in 6MWD, increase in time to clinical worsening as well as improvement in WHO functional class in the active treatment group (88).

– Nitric oxide pathway stimulation

The efficacy of sildenafil and tadalafil for treatment of PAH were evaluated in two controlled trials - Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study and Tadalafil in the Treatment of Pulmonary Arterial Hypertension PHIRST trial (89, 90). Both showed trends towards improved exercise capacity and increased time to clinical worsening, although results did not reach statistical significance. While these agents slow breakdown of cGMP, a secondary messenger for NO, an important endogenous vasodilator, riociguat, an orally active guanylate cyclase agonist, which directly stimulates cGMP production, rather than slowing breakdown, was demonstrated to benefit significantly cardiac haemodynamics, exercise capacity and time to clinical worsening and was recently licensed for treatment of PAH (91).

– Combination therapy

As multiple studies have demonstrated the improved efficacy of different combinations of the used advanced treatments compared to monotherapy, the current American College of Chest Physicians (ACCP) and European Society of Cardiology (ESC) guidelines for treatment of PAH recommend the use of combination therapy in patients unresponsive to monotherapy (83).

– Immunosuppression in SSc-PH

Although a recent prospective, randomised, placebo-controlled trial of Imatinib in PH patients already on advanced treatments demonstrated improvement in 6MWD and haemodynamics in the active arm, side effects were very frequent and a third of the patients had to discontinue the drug (92). In SSc-PH patients immunosuppression is considered only in the context of SLE or vasculitis overlap.

Treatment for cardiac involvement

Clinically significant cardiac complications in SSc are rare. Apart from supportive therapies, immunosuppressants are used when there is evidence of myocarditis with development of heart failure. Large pericardial effusions may require fenestration.

Treatment of renal crisis

SRC can be triggered by high doses of corticosteroids and treatment with nephrotoxic drugs, such as cyclosporine, therefore those should be avoided in SSc patients, especially those with diffuse subset and anti-RNA polymerase antibody, who can be at particular risk of this complication (63, 93). The use of ACE inhibitors has revolutionised the management of SRC leading to substantial reduction in mortality and much lower proportion of patients requiring long-term dialysis (94). After

SRC, renal function may continue to improve for up to 18 months, therefore renal transplantation should not be considered until at least 2 years from the crisis onset have elapsed (95).

Outcome assessment

While SSc is a chronic condition with a specific disease course, there is a great inter- and intra-patient variability in symptoms (96). This makes measures of disease an essential tool used both in clinical practice and for research purposes. Establishing reliable outcome measures for clinical trials has been particularly challenging, as it is often impossible to judge whether changes are related to treatment or are part of the natural history of the disease.

Activity and severity

Activity and severity are aspects of SSc that are often difficult to distinguish. Experts have agreed that severity refers to the overall effect of the disease on different organ systems. It has irreversible component, termed damage, and reversible component, described as activity (97). The European Scleroderma Study Group initiated a one year multicentre study to define criteria for disease activity and this resulted in the development of a preliminary activity index (98-100). This was recently assessed for construct validity with exploration of additional markers of disease activity, particularly ones related to lung disease (101). A severity score was also initially developed and internally validated by Medsger *et al*. and subsequently revised by an international committee (97, 102).

Quality of life

There are multiple tools used to assess the effect SSc has on function, including activities of daily living, social and emotional wellbeing. Some of the more commonly used include Scleroderma Health Assessment Questionnaire (SHAQ) (103), SSc functional score (SSc-FS) (104, 105), Scleroderma Gastrointestinal Tract Questionnaire (SSc-GIT) (106, 107), Mouth Handicap in Systemic Sclerosis (MHISS) scale (108), Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) (109) and Raynaud's condition score (RCS) (110). Newer indices, including Combined Response Index for Systemic Sclerosis (CRISS) and Outcome Measures in Pulmonary Arterial Hypertension Related to Systemic Sclerosis (EPOSS) are being developed in accordance with the OMERACT (Outcome Measures in Rheumatology) process (111).

Detection of new complications and recommendations for management

One of the most important factors in long term management of SSc of both subsets is systematic investigation of cases to detect organ-based complications as early as possible, so that treatment can be initiated. These complications can affect both subsets and in general, PF, SRC and cardiac scleroderma develop mostly within the first 5 years of disease (9, 112). On the other hand, PH and gastro-intestinal involvement can develop throughout the disease course, and in many patients are a late complication (96, 112). This requires greater vigilance, closer and more frequent follow-up early in the disease course while warranting continuous regular echocardiography and pulmonary function testing (PFT) in subjects with long-standing SSc.

The approach to management of a patient with SSc depends greatly on disease subset, duration and organ involvement. Full clinical assessment, including serological profile, chest x-ray, PFTs, echocardiography and ECG are mandatory in every new SSc patient. Treatment depends on the active problems and immunosuppressive agents are used only if there is active, progressive skin or organ disease, or in the context of overlap syndromes. In general, patients with early (<3 years) dcSSc require immunosuppressive treatment and if no significant organ disease is present, oral immunosuppression with MMF or MTX is preferred. In lcSSc patients, as well as in dcSSc patients with late disease and stable skin involvement, immunosuppression is not necessary, unless there is organ involvement. Based on history and initial test results, patients at risk of various organ complications can be identified and further tests, such as high resolution CT scanning, right heart catheterisation or cardiac MRI may be indicated. Unless progressively symptomatic, patients usually do not require repeat basic tests more often than yearly. If organ disease is present, this directs the choice of immunosuppressive agents. In patients with PF, where FVC is ≥70%, MMF is normally used, while for more extensive lung disease ivCYC given as six monthly pulses is more appropriate. In patients unresponsive to treatment with MMF or ivCYC, Rituximab could be used. Patients with myocarditis are normally treated with ivCYC or MMF. In the context of SRC, if immunosuppression is required, low dose of MMF could be used. When features of an overlap syndrome are present, immunosuppressive treatment appropriate for the overlap features can be chosen.

In the majority of patients, DMARDs are discontinued after several years when disease stabilises, while treatment of vascular and gastro-intestinal complications are often lifelong.

Conclusions

Regular disease monitoring with internal organ tests has led to improved recognition and earlier diagnosis of organ problems. Although none of the current treatment strategies has been shown to improve survival of SSc patients in prospective controlled trials, there is clear evidence of reduced mortality over more recent decades (113, 114), validating the current approach to disease management.

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