Review Article

Emerging Evidence-based Therapies for Systemic Sclerosis

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Abstract

Systemic sclerosis (SSc) (scleroderma) is an uncommon multisystem connective tissue disease with high unmet need and mortality. There has been an improvement in overall outcome and survival over the past three decades, but it still has the highest mortality among any of the autoimmune rheumatic diseases. Progress in its management has come through more organized assessment and treatment together with the emergence of therapies that can target specific complications of the disease such as renal crisis and pulmonary arterial hypertension. In addition, there is a growing understanding of pathogenesis that allows more targeted approaches to therapy to be explored in clinical trials. In this review, several aspects of SSc management including the more targeted therapies including strategies to block specific pathways or mediators have been discussed.

Key Words: *Immunosuppressants, scleroderma, systemic sclerosis, therapies, treatments*

Introduction

Systemic sclerosis (SSc) is an uncommon multisystem connective tissue disease with three main pathogenetic components – immunological, microvasculopathy, and tissue fibrosis. The key histological features of SSc are indicated in Figure 1 and provide a template for the aspects of the disease that need to be addressed to achieve therapeutic success in the skin and internal organs affected by SSc. High burden of disease morbidity and mortality is seen among SSc patients with or without major organ involvement. Over the past few decades, despite some data showing improvement in the trend in mortality in SSc patients, the mortality risk remains high with cardiopulmonary involvement as a leading cause.[1,2] High prevalence of SSc-related causes of mortality was observed in the EULAR Scleroderma Trials and Research (EUSTAR) cohort involving 284 fatalities, also mainly attributed to cardiopulmonary causes.[3]

The 10-year survival rate, however, has improved significantly in those with scleroderma renal crisis (SRC) with the introduction of angiotensin-converting enzyme (ACE) inhibitors in the 1980s.[1] The outcome in SSc patients was also found to be improving with increased awareness and ascertainment of organ-based complications, particularly lung complications.[4] In the future, prediction models for organ complications can be a useful tool for patient risk stratification and to predict long-term outcome of SSc.[5] Together with this, it is crucial to treat the manifestations in the earliest stage possible for a better prognosis, outcome, and survival. The therapies which target specific organ manifestations have emerged over the years from intensive research studies and clinical trials, in addition to a growing understanding of pathogenesis in SSc. This article reviews the general approach to management and highlights areas that are improving based on the results of recent clinical trials. In addition, the prospects for more targeted therapies including strategies to block specific pathways or mediators are reviewed. The potential links between different components of pathogenesis in SSc mean that it is likely that more specific targeted therapies may have beneficial effects on more than one aspect of the disease.

Emerging Support for Broad-spectrum Immunosuppression

Although the pathogenesis of SSc is complex and multifaceted, it is clear that altered immunological reactivity is an important component of the disease. Thus,

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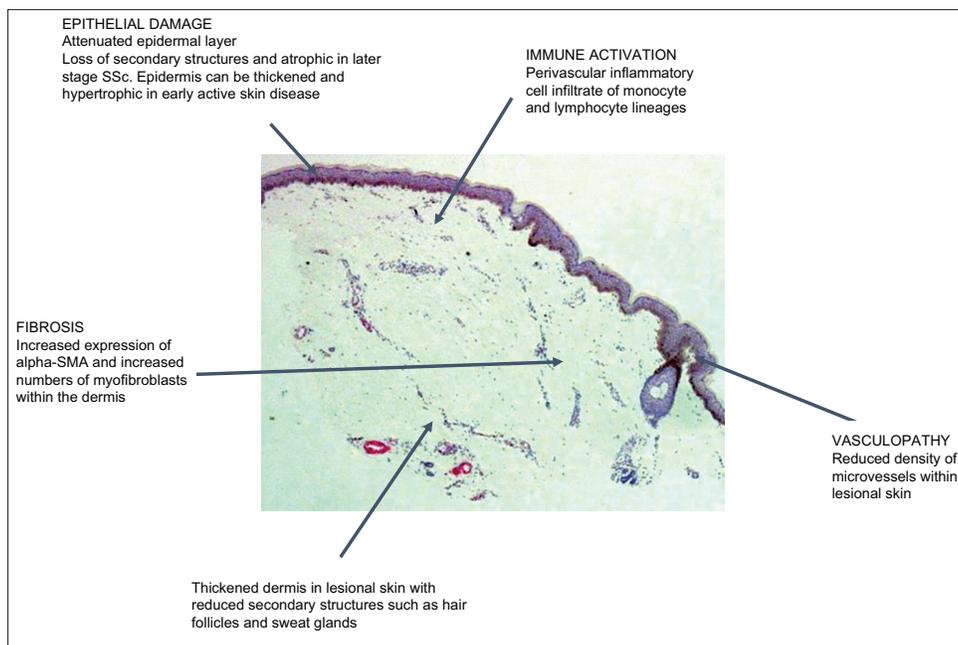
Figure 1: Pathological hallmarks of lesional skin in systemic sclerosis. Systemic sclerosis leads to damage of epithelial, vascular and dermal structures within the skin. Inflammation is generally perivascular and more prominent in early stage disease but is much less prominent than in some other skin diseases including localized scleroderma (morphea). The consequences of these processes are dermal fibrosis. Similar changes in internal organs underlie the major burden of disease including both life-threatening and nonlethal manifestations

genetic studies as well as examination of tissue samples and cultured cells for patients all point to abnormalities in both innate and adaptive immune systems. In this context, it is striking that immunosuppression is the most widely used approach for treating SSc and major complication such as lung fibrosis. There is an increasing evidence base to support this, and the results of several key recent studies are summarized below. Conventional disease-modifying therapies have shown to be beneficial in the treatment of SSc. These broad-spectrum immunosuppressants are often used as organ-based therapy and are outlined below.

Cyclophosphamide

Cyclophosphamide is an alkylating agent that produces immunosuppressive effects possibly through a cytotoxic effect on lymphocytes. Cyclophosphamide has shown to be efficacious in the treatment of SSc interstitial lung disease (ILD). In the Scleroderma Lung Study I (SLS I), treatment with oral cyclophosphamide showed significant beneficial effect on both lungs and skin compared to placebo.[6] Similarly, the FAST study suggests that cyclophosphamide is beneficial for lung function over 1 year in SSc patients.[7] Cyclophosphamide is also given in patients with rapidly progressive fibrotic activity, either in skin or lungs.

Mycophenolate mofetil

Mycophenolate mofetil (MMF) interferes with T- and B-cell proliferation by acting as a potent inhibitor of the enzyme inosine monophosphate dehydrogenase. The use of MMF is encouraging for manifestations of skin, lungs, and muscles with reasonable tolerated gastrointestinal symptoms.[8-10] MMF was used in several studies for induction, for maintenance, for both induction and maintenance.[10] A recent landmark study, SLS II trial's (MMF vs. oral cyclophosphamide) preliminary analyses, showed comparable improvement in forced vital capacity (FVC) in both treatment groups.[9]

Methotrexate

Methotrexate (MTX) is an antimetabolite that has shown not only reduction of proinflammatory cytokine production but also inhibition of antigen-induced T-cell activation and adhesion molecules.[11] Improvement in skin scores was observed in several randomized control trials (RCTs) and has been recommended by EULAR-EUSTAR experts as an option for the treatment of skin manifestations of early diffuse SSc.[12-14]

Rituximab

The therapeutic concept of B-cell depletion in SSc provides a better-defined treatment and evidence-based following demonstration of clinical efficacy in observational studies and open-label trials.[15,16] In tight skin (*tsk*) mice, the CD20 monoclonal antibody has shown to reduce profibrogenic cytokines such as transforming growth factor-β (TGF-β) and significantly suppress skin fibrosis.[17] Interestingly, autoantibody production and hypergammaglobulinemia were also suppressed following B-cell depletion in the mouse model. In SSc patients, rituximab has shown beneficial effects in fibrotic activity of skin and prevention of worsening of lung fibrosis,[18] suggesting that B-cells and

autoantibodies are the primary drivers of fibrosis in skin and lung tissue. Significant improvement in pulmonary function was demonstrated in case–control analyses, with promising results where rituximab could be considered as a treatment option in patients who are not able to tolerate cyclophosphamide or have contraindication for it. However, further research is needed while awaiting validation for efficacy of rituximab in an RCT.

Autologous hematopoietic stem cell transplant

Autologous hematopoietic stem cell transplant (ASCT) is a promising emerging therapy for the management of SSc after several studies including Phase I and Phase II trials have shown efficacy in a subgroup of SSc patients with poor prognosis. Positive outcomes were observed in reversal of skin fibrosis, improvement in lung function, quality of life, and functional ability.[19-23] The phase II ASSIST trial compared safety and efficacy of autologous nonmyeloablative ASCT in diffuse cutaneous SSc (dcSSc) to a control group that received six cycles of monthly intravenous cyclophosphamide. Both mRSS and FVC improved significantly for up to two years in the group that received ASCT.[24] In the ASTIS phase III study, ASCT conferred a significant long-term event-free survival benefit in SSc patients despite an early treatment-related death of 10.1% and increase in serious adverse events.[23] This treatment is considered for SSc patients with early diffuse cutaneous disease who have a poor outcome. Safer transplant regimens and better patient selection may improve the outcome of ASCT for SSc. The ongoing SCOT trial is much awaited and would be important to further determine the efficacy and safety of ASCT in SSc.[25]

Other immunomodulatory strategies

Antithymocyte globulin

Antithymocyte globulin (ATG) has been long used in the treatment of renal allograft rejection and induction agent for kidney transplantation. ATG has been studied in small open-label trials and found to have mixed results.[26-28] The overall outcome of this treatment is discouraging including adverse reaction of serum sickness.

Aimspro® (anti-inflammatory immunosuppressive product) (hyperimmune caprine sera (HICS))

A novel agent, hyperimmune goat serum, Aimspro conferred potential benefit for skin fibrosis in established dcSSc with no safety concerns in a recent Phase II RCT conducted.[29]

Oral collagen

Experimental evidence demonstrated identification of a variety of autoantigens in SSc patients,[30-32] including type I collagen leading to trials that have demonstrated successful treatment with orally administered bovine type I collagen. Late-phase dcSSc patients treated with oral collagen

experienced a significant reduction in the mRSS compared with that in the placebo-treated patients in a subanalysis of data from an RCT study involving 168 dcSSc patients.[33] In addition to improvement in skin fibrosis, an open-label study reported significant reductions in interferon-γ, interleukin (IL)-10 in peripheral blood mononuclear cells culture supernatants, and sIL-2r levels following oral administration of type I collagen in SSc patients suggesting reduction in T-cell reactivity to human type I collagen.[34]

Intravenous immunoglobulin

Intravenous immunoglobulin (IVIG) is generally considered a safe immunomodulatory therapy used for a wide range of immune-mediated conditions. The use of IVIG in SSc has been studied in both *tsk* mouse models and patients with SSc focusing on skin fibrosis and inflammatory myopathy overlap in SSc.[35-37] Following administration of IVIG in SSc *tsk* experimental models, downregulation of type 1 procollagen with decreased collagen deposition was observed. In addition to modulation of metalloproteinase activity, inhibitory effects on IL-4 and TGF-β were also reported.[38,39] Interesting data from a recently published observational study revealed sustained beneficial effect of IVIG in established gastrointestinal complications in SSc patients.[37]

Treatment of vascular complications

Endothelin receptor antagonist

Endothelin-1 (ET-1) is a potent vasoconstrictor implicated in the development of vascular dysfunction and cardiovascular disease. Proliferative vascular remodeling properties lead to complication of pulmonary arterial hypertension (PAH) when overexpression of ET-1 results in abnormal growth pattern of endothelial cells, smooth muscle cells, fibroblasts, and pericytes.[40,41] Given the prominent role of the endothelin system in PAH, a variety of endothelin receptor antagonist (ERA) agents are used in the treatment of PAH in SSc.[42,43] Bosentan, a dual ERA of both ET (A) and ET (B) receptors, is licensed in the treatment of PAH in SSc and improves survival.[44,45] The RAPIDS-2 study reported an additional benefit of bosentan for the treatment of reducing the number of new digital ulcers even though beneficial effect was not seen on the healing of preexisting digital ulcers.[46] Further encouragement for the targeting of endothelin comes from other agents, including ambrisentan and macitentan.[47-49] In addition, there is evidence that combination of bosentan with sildenafil may have a better treatment effect from one small recent study.[50]

Phosphodiesterase 5 inhibitor

Nitric oxide has an important role as a mediator of endothelium-dependent vasodilation and its production is impaired in PAH. Sildenafil, through phosphodiesterase V, inhibits cyclic guanosine

monophosphate degradation resulting in increased level of nitric oxide. Data from the Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) study suggest that sildenafil at a dose of 20 mg improved exercise capacity (6-minute walk distance [6MWD]), hemodynamic measures, and functional class after 12 weeks of therapy.[51] Clinical studies have reported positive encouraging results for the treatment of sildenafil in vascular complications of SSc such as PAH, Raynaud's phenomenon, and digital ulcers.[52,53] There is evidence that sildenafil may benefit digital ulcer disease in SSc[50] and it is used, as are other drugs in this class, to treat this complication of SSc.

Tadalafil is another oral phosphodiesterase 5 inhibitor (PDE5-i) approved for the PAH treatment. Improvement in 6MWD and its sustained results were observed in the Pulmonary Arterial Hypertension and Response to Tadalafil Study trial.[54] Upfront combination therapy with ambrisentan and tadalafil also significantly improved hemodynamics, right ventricle structure and function, and functional status in treatment-naive patients with SSc-PAH.[55] The study of tadalafil for the treatment of ILD in SSc is completed.[56]

Prostacyclin

Iloprost is a prostacyclin analog with dual vasodilatory and antiplatelet inhibitory effects. Several studies have reported efficacy of parenteral iloprost in the treatment of vascular manifestations in SSc, particularly Raynaud's phenomenon and healing of digital ulcers.[57-60] Epoprostenol, another intravenous preparation of prostacyclin, is approved for the treatment of PAH. Patients were also noted to have fewer digital ulcers compared to those without this therapy.[61] The efficacy of the oral formulation of treprostinil compound has also been studied in an open-label study.[62] Interestingly, a pilot study to evaluate the safety and efficacy of oral treprostinil in the treatment of calcinosis in SSc patients is underway.[63]

Riociguat

Clinical trials have looked at the oral drug riociguat, a soluble guanylate cyclase stimulator, as a new approach to treat pulmonary hypertension.[64-66] It is now licensed for chronic thromboembolic pulmonary hypertension and also for PAH including SSc-associated disease. There is the possibility based on preclinical studies that riociguat may also have some broader antifibrotic benefit, and this is being assessed in the ongoing RISE-SSc study (Riociguat Safety and Efficacy in patients with dcSSc). This clinical trial has been initiated to evaluate the efficacy of riociguat on skin, lungs, and digital ulcers on SSc patients. This study will include 130 patients at more than 60 sites in 15 countries.[67]

Angiotensin-converting enzyme inhibitor

SRC was once the most common cause of mortality in SSc. The 10-year survival rate has improved significantly with the introduction of ACE inhibitors in the 1980s.[1] Contributing risk factors of developing SRC are diffuse cutaneous or rapidly progressive forms of SSc, treatment with high dose of corticosteroid and presence of anti-RNA polymerase III antibody.[68] Patients on ACE inhibitors (captopril or enalapril) had a significantly better survival rates, up to 90% at 5 years and 85% at 8 years.[69,70] The need for permanent dialysis too decreased following treatment of ACE inhibitor in SRC. Prophylactic ACE inhibitors have not been shown to improve outcomes.

Other therapies

The use of fluoxetine, a selective serotonin reuptake inhibitor, reduced the Raynaud's phenomenon attack frequency and severity.[71] Losartan (an angiotensin receptor blocker) showed greater improvement in both primary and secondary Raynaud's phenomenon symptoms when compared to nifedipine.[72] Interdigital injections of botulinum toxin and sympathectomy are used in resistant cases.[73,74] The first randomized, placebo-controlled trial on the use of botulinum toxin to treat Raynaud's phenomenon in SSc patients is ongoing.[75]

Challenging aspects of the disease – nonlethal burden

With the advances in treatment and improved survival from better management of life-threatening complications, the nonlethal aspect of SSc becomes an important aspect of the disease even though it is hard to treat with the challenges remain. This is important since it is often these aspects of the disease that patients find most challenging. In addition, it is likely that some of the emerging disease modifying treatments may benefit broader aspects of the disease, and so they should continue to be assessed in clinical trials and also receive focus in basic laboratory research.

Digital ulcers

Patients with digital ulcers have significant cost and disease burden including impairment in productivity and daily activity. The higher disease burden is reported to be experienced by SSc patients with recurrent and chronic digital ulcers compared with patients with no digital ulcers and episodic digital ulcers.[76]

Fatigue

Fatigue is a disabling and difficult-to-manage problem. Severe fatigue is present in 41–57% of patients with rheumatic disease including SSc.[77] Fatigue and pain should be taken into account in the management of SSc. Graded exercise which is matched to patient's physical abilities could help improve patient's physical functioning and reduce fatigue. Solving sleep problems or changing negative coping behavior could also help patients to have less fatigue.[78]

Pruritus

Pruritus is a common problem in SSc with higher rate occurrence in early disease. Greater skin involvement and greater gastrointestinal involvement were reported to be independently associated with pruritus.[79] Unfortunately, pruritus has limited treatment options in this disease. The use of low-dose naltrexone hydrochloride in its treatment is encouraging from case series reports.[80]

Calcinosis

Medical benefit of calcinonsis in SSc is limited. An open-label study demonstrated that minocycline is a potentially useful drug in the treatment of calcinosis in SSc. The mechanism of action proposed is may be mainly through matrix metalloproteinases inhibitory activity and anti-inflammatory effects. Calcium binding properties and antibacterial actions may also have a role.[81]

Psychosocial issues

The psychological consequence in patients with SSc is increasingly recognized.[82,83] Emotional burden such as depression and anxiety is common among SSc patients. While in some studies, depressive symptoms were shown to be independently associated with severity and physical functioning of the disease such as pain and fatigue,[84-86] other studies did not reflect the above findings.[78,87,88] Some studies also included psychological measures such as cognition acceptance and emotional or social support received and found these to be independently associated with depressive symptoms.[86,87] Focus should be given by clinicians to treat the psychosocial aspect of the disease and should be integrated into interdisciplinary care.

Facial appearance

The changes in facial appearance and hands have an effect on appearance self-esteem and body image satisfaction.[89] Depressive symptoms are also recognized in addition to psychosocial impairment in SSc population.[90] The physical change in SSc patients also affects sexuality, especially in females.[91] The brief-satisfaction with appearance scale (Brief-SWAP) has been validated for SSc.[92]

Sexual dysfunction

Sexual dysfunction is a concern for both male and female SSc patients and has a major contribution to nonlethal burden of disease.[91] Erectile dysfunction is seen in up to 81% sexually active SSc male population.[93-95] As a first-line pharmacological treatment option, PDE5-i should be considered for the treatment of erectile dysfunction. Female sexual dysfunction (FSD) is significantly more prevalent than in the general population. Multiple factors contribute to FSD in terms of psychological and physical components and this may interfere with sexual act. Body image as a consequence of skin fibrosis is an important predictor of FSD; however, it is reported to be less important than pain in determining sexual function.[96] In SSc, psychological burden and emotional burden such as depressive symptoms and marital distress were associated with impaired sexual functioning in SSc.[97,98] Evaluation of strategies and development of intervention to improve the overall sexual functioning are important to address this issue. A referral to a specialist may be warranted.

Work disability

Work disability continues to be a major burden in individuals with rheumatic diseases including SSc and accounts for a large fraction of its costs. It has been shown to be prevalent even in early disease of SSc.[99] Clinical manifestations such as lung involvement, fatigability, pain, diffuse disease, disease duration, and severity were reported to correlate with work disability.[99,100] SSc patients with psychosocial factors and less social support too tend to have association with work disability.[100]

Management of gastrointestinal complications

Proton pump inhibitor

Gastroesophageal manifestations are seen in up to 90% of SSc patients with increased frequency of gastroesophageal reflux disease (GORD) and esophageal dysmotility contributing to morbidity of the disease.[101] Besides lifestyle modification and avoidance of aggravating factors, proton pump inhibitor (PPI) either a single or double dose helps relieve symptoms of GORD. The traditional PPIs available include omeprazole, lansoprazole, pantoprazole, and rabeprazole.[102,103] H2-receptor antagonists can be added if symptoms of GORD persist despite on PPIs. These agents are usually added at bedtime for overnight symptoms as nocturnal acid secretion is influenced by histamine secretion.[104,105]

Prokinetics

Prokinetics are mainstay of treatment for esophageal dysmotility and gastroparesis.[106,107] It is recommended when patients have persistent symptoms of dysphagia, poor acid control of GORD, or symptoms of delayed gastric emptying. Examples of prokinetics used are metoclopramide, dopamine receptor antagonist domperidone, and the macrolide antibiotic, erythromycin. Prokinetics must be used with caution in view of risk of cardiac arrhythmias.[108]

New dysmotility agents

A novel agent serotonin (5-HT4) receptor agonist, prucalopride, was shown to have remarkable prokinetic properties resulting in improvement in gastroenteric transit and functional constipation.[109] A randomized placebo controlled drug trial is currently ongoing.[110]

Sacral neuromodulation and posterior tibial nerve stimulation

Fecal incontinence in SSc patients is a challenging condition to treat and has a considerable impact on patient's quality of life. The use of conventional methods is often unsuccessful. Sacral neuromodulation is a well-established treatment for refractory cases of fecal incontinence; however, mixed results are reported from case series on its efficacy in treating fecal incontinence in SSc including poor medium term efficacy.[111,112] Posterior tibial nerve stimulation (PTNS) is an alternative to modulate the sacral plexus indirectly. Preliminary data demonstrated significant effects of PTNS in the treatment of fecal incontinence in SSc in a recently conducted RCT.[113]

Recent clinical trials and emerging treatments

Lysophosphatidic acid 1 antagonist

Lysophosphatidic acid (LPA), a lysophospholipid mediator, is derived from stored lipid precursors and is found to be elevated in the sera of SSc patients, providing a rationale in considering a targeted therapy in SSc.[114] The antifibrotic effect of LPA1 on dermal and lung fibrosis is supported in mouse models.[115,116] Promising results were seen in a study that used a novel orally active LPA1 antagonist demonstrating inhibition of lung fibrosis in bleomycin-induced mouse model via reduction of vascular leakage, tissue injury, and profibrotic cytokine production.[117]

Tocilizumab

Tocilizumab is an IL-6 receptor blocker. High levels of IL-6 expression was found in sera and dermal fibroblast of SSc patients, implicating the role of IL-6 in the pathogenesis of SSc. Studies also demonstrate associations with progression of lung fibrosis and survival.[118-120] The clinical benefits of tocilizumab in SSc is by direct blocking of the profibrotic property of IL-6 on fibroblasts and by suppression of inflammation through tolerance regulatory T-cell upregulation and reduction of the polarization of pathogenic Th17 cells.[120] The safety and efficacy of tocilizumab in adults with SSc was explored in the faSScinate trial. The week 48 data suggest a positive risk/benefit profile for tocilizumab in SSc in terms of skin fibrosis, patient-reported outcome, and pulmonary function, supporting further assessment on the use of tocilizumab in SSc patients.[121] A large phase III clinical trial is underway to confirm and extend data about the potential efficacy of this agent in early stage diffuse SSc with evidence of an increased acute phase response.

Pirfenidone

Pirfenidone is an orally active small molecule with anti-inflammatory and antifibrotic actions. Pirfenidone modulates cytokines and growth factors, particularly suppressing TGF-β.[122] In an open-label trial of pirfenidone in SSc-ILD, mixed results in pulmonary function and minor changes in mRSS were reported. Pirfenidone was generally tolerated.[123]

Nintedanib

Nintedanib is a tyrosine kinase inhibitor that has recently been demonstrated to reduce the decline in FVC, and hence slow down the disease progression in idiopathic pulmonary fibrosis.[124] Its efficacy as a potent antifibrotic agent has now shown to be evident in mouse models of SSc.[125] A phase III clinical trial, SENSCIS, is underway which would allow exploration of the treatment Nintedanib in patients with SSc-ILD that may prove to be effective.[126]

Fresolimumab

The human monoclonal antibody fresolimumab targets all three TGF-β isoforms. The effect of this drug on expression of molecular markers in the skin and on skin scarring was evaluated in SSc patients after a brief duration of 7 weeks treatment. Rapid inhibition of TGF-β regulated gene expression and improvement in the mRSS skin score in response to Fresolimumab provides further encouraging data on TGF-β as a potential targeted therapy in SSc.[127]

Concluding comments

Although outcome of some aspects of SSc is improved, there remain major challenges. As there is better treatment of complications, other manifestations emerge to challenge patients and physicians. In addition, there is a much clearer understanding of the abnormal biology underlying SSc and this permits more logical choices to be made in selecting new candidate therapies and linking them to the most promising disease manifestations. Figure 2 summarizes the multiple ways in which pathobiology may be targeted for disease modification. There has been clearer progress in diffuse SSc, and so limited disease now represents an important challenge. In addition, the nonlethal burden of the disease needs to be tackled as people are living longer with the diagnosis rather than dying early for the most severe complications of SSc. Symptoms such as fatigue, pruritus, anorectal incontinence, and calcinosis remain an enormous unmet medical need. Since SSc is an orphan indication, it will hopefully see disproportionate progress over the coming years. The recent results from trials and development of promising phase II studies offer hope that within the next few years more effective and better tolerated treatments for SSc and its major manifestations will merge.

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Conflicts of interest
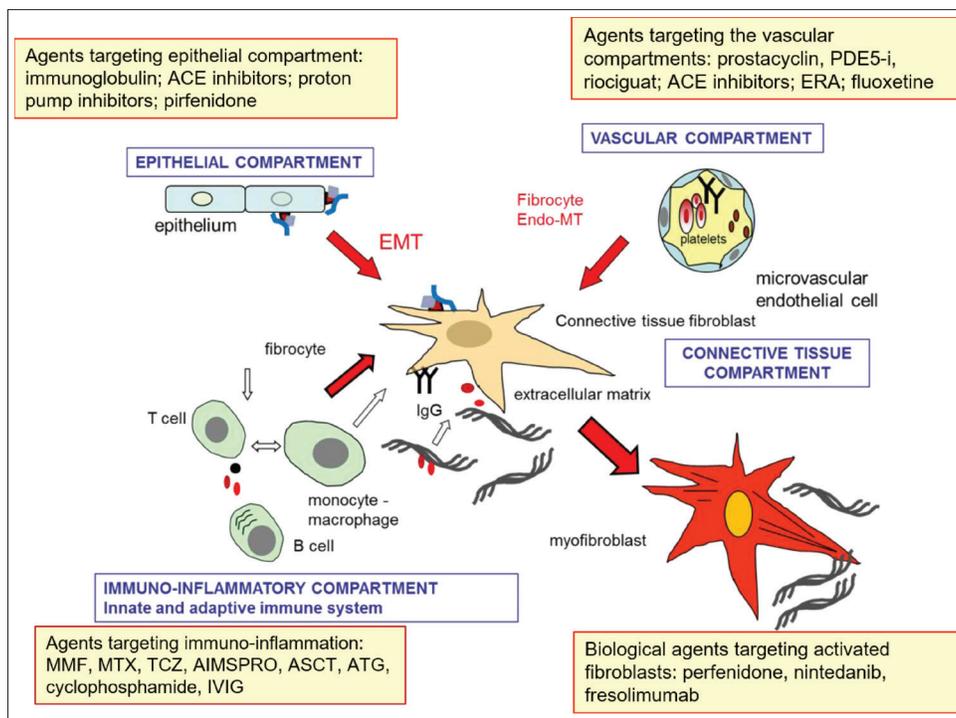
There are no conflicts of interest.

Figure 2: Targeting of systemic sclerosis pathogenesis: Strategies for disease modification. The key cellular players implicated in the pathogenesis of systemic sclerosis that underlie the classical histopathological feature of the disease are indicted together with some of the established and emerging treatment options that may permit disease modifying therapy that may potentially impact upon the multiple facets of pathobiology

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