Therapeutic trials for systemic sclerosis: An update

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ABSTRACT

The pathogenesis of systemic sclerosis (SSc) is complex, and the final story is yet to be elucidated. The clinical heterogeneity of the disease, its various autoimmune and antibody profiles, its long course and tendency for spontaneous cure makes the design of clinical trials difficult. The overwhelming need in this disease is to diagnose it early and identify those patients who will benefit most from early, aggressive treatment. We attempt to review data from recent clinical trials and the lessons derived.

Key Words: New drugs, Scleroderma, Trials

DEFINITION

Scleroderma is derived from the Greek words *skleros* (hard or indurated) and *derma* (skin). It was initially defined by Hippocrates, but a detailed description was given by Carlo Curzio.[1]

PATHOGENESIS

It is an autoimmune disorder that involves interaction of three pathogenetic factors: vasculopathy of small arteries and capillaries, fibrosis, and immunologic damage.

Systemic sclerosis (SSc) is characterized by tissue fibrosis, obliterative microangiopathy, and immune abnormalities[1].

The role of autoimmunity in generating the clinical and pathologic phenotype in SSc remains uncertain.[1,2] The process starts with microvascular change and endothelial cell activation, which is followed by inflammation and immune cell activation, with a perivascular infiltration of inflammatory cells initially from the innate immune system and including cells of the monocyte/macrophage lineage.[1,2] Later, there is evidence of involvement of the adaptive immune system.[2] Lymphocytic infiltrates are noted, including T cells bearing markers of activation.[2-4] Recent studies have also identified B-cell genetic signature.[2,3]

As the disease progresses, there is evidence of a profibrotic fibroblastic cell population becoming established within the skin.[2,3] This leads to increased extracellular matrix deposition.[2-4] As the disease becomes well established, lesional skin becomes relatively avascular; and after 12 to 18 months, there is often little evidence of ongoing inflammation. This suggests that there are probably distinct phases, at least in the skin, when the component processes of SSc might be amenable to therapeutic modulation.[2,3] The production of various cytokines consequent to vessel damage, intimal hyperplasia, and platelet aggregation lead to contraction of the vessels, which causes obliterative microangiopathy[1,2].

Thus, targeted therapy is likely to depend critically on the disease stage and subset.

There is a complex interaction between multiple cell types during the evolution of SSc.[2-4] These cell types may interact through direct contact, but soluble mediators are also likely to be critical.[2,3] These regulate cell migration, differentiation, and proliferation. Cellular origins may

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be diverse within lesional tissue, and there has been a recent focus on the role of progenitor cells locally or migrating from other sites, such as bone marrow or from peripheral blood.[1,3,4] The myofibroblast is the effector cell for fibrosis and many other organ-based changes.[1,2] Myofibroblasts are likely to be derived from at least three sources: local fibroblasts, transdifferentiation, and other cell types.[1,2] Circulating and locally produced soluble mediators regulate this process.[1,2] The key patterns of intercellular interaction that operate in SSc pathogenesis are summarized.[1,2]

Treatment of systemic sclerosis has been somewhat haphazard, and treatment has often been 'borrowed' from the experience gained from treating other connective tissue diseases.[1,2] There was a period of time that was focused mainly on organ-specific manifestations of systemic sclerosis, and some advance in preventing vital-organ damage (such as renal crisis) was achieved.

At present, there are no treatments that are known to change the overall course of SSc.[2,3]

Survival has improved dramatically in recent years and is due to the effectiveness of treatments directed at specific internal organ features. These include drugs for pulmonary hypertension (epoprostenol, treprostinil, bosentan); renal involvement (angiotensin-converting enzyme inhibitors); and pulmonary inflammation (cyclophosphamide).[2-4]

Clinical research on therapies for scleroderma is currently very active. The choice of therapy is complex and depends on the type of SSc (diffuse versus limited); the stage of illness (early versus late); and the specific organ-related problems faced by the individual patient.[1,3-5]

The future and present trials would focus on the cellular mediators in systemic sclerosis as potential therapeutic targets[2] [Table 1].

Our focus will be on the potentially positive, negative, and open enrollment trials in SSc.

Table 1: A summary of the potential therapeutic agents and target pathways modified by them

Candidate therapy	Target pathway
Bosentan	ETA/ETB pathway
Imatinib	PDGF receptor signalling
Infliximab	TNF-α
Adalimumab	TNF-α
Etanercept	TNF-α
CAT-192	TGF-β1
GC-1008	TGF-β1, TGF-β2, TGF-β3
FG-3019	CTGF ligand
Alefacept	LFA3/CD2
Basiliximab	IL-2Rα
MLM-1202	CCR2
Efalizumab	LFA/ICAM-1

CCR, CC chemokine receptor; ETA/B, endothelin receptor subtype A/B; CTGF, connective tissue growth factor; ICAM, intercellular adhesion molecule; IL-2Rα, interleukin-2 receptor α; LFA, lymphocyte function associated; PDGF, platelet-derived growth factor; TGF, transforming growth factor; TNF, tumor necrosis factor.

Table 2: Major trials with bosentan

Bosentan: BUILD-2 trial (Bosentan in Interstitial Lung Disease in Systemic Sclerosis-2)	No Difference
RAPIDS-1 and RAPIDS-2 (bosentan in digital ulcers) (RAndomized Placebo-controlled Investigation of Digital ulcers in Scleroderma)	Better than Placebo

TRIALS COMPLETED: POTENTIALLY POSITIVE RESULTS

Bosentan [Table 2]

Bosentan is the first orally active, high-affinity endothelin dual receptor antagonist approved for the treatment of pulmonary arterial hypertension.[1-4] Elevated circulating levels and increased tissue expression of endothelin-1 are characteristic of SSc, and patients demonstrate endothelin receptor overexpression in affected tissues and organs.[2-4]

Two randomized trials have demonstrated that bosentan is effective in idiopathic pulmonary arterial hypertension and in pulmonary arterial hypertension related to connective tissue diseases.[5,6]

Oral bosentan 125 mg twice daily in improving exercise capacity has been demonstrated in well-designed trials in adult patients with idiopathic pulmonary arterial hypertensions (PAH) or PAH associated with connective tissue disease or congenital systemic-to-pulmonary shunts, and in other trials in patients with idiopathic PAH or PAH associated with congenital heart disease or HIV infection.[5,6] The beneficial effects of bosentan treatment may be maintained for up to 1 year in patients with idiopathic PAH or PAH associated with connective tissue disease.[7]

Despite the potential for treatment-related teratogenicity and hepatotoxicity, long-term data indicate that bosentan is generally well tolerated at the approved dosages.[5]

Although well-designed trials are required to establish the efficacy of bosentan versus, or in combination with, other specific PAH therapies, especially sildenafil, the convenient oral administration and lack of serious injection-related adverse effects may render bosentan preferable to other PAH therapies.[4] Preliminary data indicate that bosentan may be effective in pediatric PAH patients, although randomized trials are required.[7]

The tolerability of bosentan is good in SSc patients.[7] The post-marketing surveillance program demonstrated that elevated liver enzymes after treatment initiation were recorded in 9.4% of the 1070 SSc patients treated with bosentan by November 19, 2004, compared with 8.4% in idiopathic pulmonary arterial hypertension patients.[7]

For digital ulcers in SSc, two randomized clinical trials supported the efficacy of bosentan for the prevention of new digital ulcers (up to almost 50% less new digital ulcers).[5-7] The treatment effect appeared more pronounced in the most severe cases (patients with three or more digital ulcers at baseline).[6,7] However, bosentan did not demonstrate beneficial effect on SSc interstitial lung disease after 1 year of treatment in a randomized, controlled study.[5,7] Whether a subgroup of SSc patients with interstitial lung disease benefits from bosentan requires further investigation. Another randomized, controlled study performed in idiopathic pulmonary fibrosis has demonstrated a treatment effect on time to disease progression or death in the subgroup with biopsy-proven idiopathic pulmonary fibrosis.[5,6]

Halofuginone

Halofuginone has been used to treat fibrosis in chronic graft-versus-host disease and scleroderma.[3,4] Chronic graft-versus-host disease (cGvHD) and systemic sclerosis share clinical characteristics, including skin and internal organ fibrosis.[8] Fibrosis, regardless of the cause, is characterized by extracellular matrix deposition, of which collagen type I is the major constituent.[2,3,8] The progressive accumulation of connective tissue results in destruction of normal tissue architecture and internal organ failure.[8] In both SSc and cGvHD, the severity of skin and internal organ fibrosis correlates with the clinical course of the disease.[8]

Halofuginone is an inhibitor of collagen type I synthesis in cells derived from various tissues and species and in animal models of fibrosis in which excess collagen is the hallmark of the disease.[6,8] Halofuginone decreased collagen synthesis in the tight skin mouse (Tsk) and murine cGvHD, the two experimental systems that show many features resembling those of human GvHD.[8] As a first step toward future treatment of internal organ involvement, an oral administration study was performed in which halofuginone was well tolerated and plasma levels surpassed the predicted therapeutic exposure.[8]

Infliximab

Patients received infliximab 5 mg/kg at weeks 0, 2, 6, 14, 22. The primary efficacy objective was to assess the change from baseline to week 26 using the modified Rodnan skin score (mRSS), SSc functional score (FS), and physician global assessment on visual analog scale (VAS).[3,4] A key secondary objective of the study was to assess safety and tolerability of infliximab in diffuse cutaneous systemic sclerosis (dcSSc). Infliximab appears to provide cutaneous disease stability and there may be short-term improvement in skin sclerosis, although significant benefit at 6 months was not demonstrated.[3,4]

Ximedon

A double-blind placebo-controlled trial was performed in 56 patients with systemic sclerosis effectiveness of a domestic drug ximedon - a pyrimidine compound - applied during electrophoresis on the affected skin, limbs.[9] The addition of ximedon-electrophoresis to the rehabilitation program for systemic sclerosis patients improved the condition in 77.8%, microhemo-circulation in 72.2%; and reduced the area of the affected skin by 9.8% ($P < 0.05$), skin induration in 55.6% of the patients.[9]

Intravenous immunoglobulin (IVIg)

Intravenous immunoglobulin (IVIg) is used to treat a number of immune-deficiencies and autoimmune diseases.[3,4] It has been shown that IVIg contains anti-idiotypic antibodies, which explains its immunomodulatory action. In murine models, recent investigations have demonstrated that IVIg can prevent, and reduce the affliction by systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), and SSc.[10,11]

A study suggested that intravenous immunoglobulins may reduce joint pain and tenderness, with a significant recovery of joint function in patients with SSc with severe and refractory joint involvement. With high-dose intravenous immunoglobulin (IVIg) at a dose of 400 mg/kg daily for 5 consecutive days, Total scleroderma score of the patient improved dramatically up to 4 weeks after IVIg (from 22 to 17 at 2 weeks and 14 at 4 weeks), and then gradually improved over 2 years (from 14 to 7).[10] The cost of intravenous immunoglobulins might limit their use only to patients who failed disease-modifying antirheumatic drugs.[11]

Methotrexate

A study on methotrexate (15 mg/week) for 6 months showed that it only provides subjective improvement.[12] A recent placebo-controlled trial of methotrexate in systemic sclerosis showed that clinical improvement following treatment was observed in 33.33% of the patients in the MTX group but none in the placebo group, but this difference was not statistically significant.[12] Thus pending further studies, its role has not been conclusively proved.

Photopheresis[13]

A randomized, double-blind, placebo-controlled trial of photopheresis in systemic sclerosis showed that photopheresis induced significant improvement with regard to skin and joint involvement in patients with scleroderma of recent onset; however, any effect when compared with sham treatment and a possible placebo effect may be modest.

PUVA/UVA-1 and phototherapy[14]

Though clinically significant effects have not been seen in systemic sclerosis, a study of low-dose UVA1, medium-dose UVA1, and narrow-band UVB phototherapy in the treatment of localized scleroderma (LS) gives hope for the cutaneous aspects of the disease.

A total of 27 patients were treated with LD (low-dose) UVA1 (20 J/cm^2), 18 patients received MD (medium-dose) UVA1 (50 J/cm^2), and 19 patients were treated with narrow –band ultraviolet B light (NB-UVB), dependent on their skin type. Phototherapy was performed 5 times weekly for 8 weeks. The reduction of the score was accompanied by an improvement of the visual analog scale for itching and tightness, histologic score, and 20-MHz ultrasound. MD UVA1 was significantly more effective than NB UVB ($P < 0.05$).

Even though holding the risk of carcinogenesis, photoaging, or UV-induced exacerbation, UVA phototherapy seems to exhibit a tolerable risk/benefit ratio, at least in systemic sclerosis, localized scleroderma, extragenital lichen sclerosus et atrophicus, sclerodermoid graft-versus-host disease, lupus erythematosus, and a number of sclerotic rarities.[15] This modality works by[3,4,15] various potential pathways, including immunomodulation of inflammation, induction of collagenases, and initiation of apoptosis.

PVAC[3]

(Potential therapeutic agent derived from, deglycolipidated *Mycobacterium vaccae*)

Use of PVAC in this pilot study of PSS appeared safe and was associated with a trend towards improved skin scores and other efficacy outcomes in the treatment group. Patients were of diffuse scleroderma and received 8 intradermal injections of 15 μg PVAC or placebo at 3-week intervals. The primary efficacy endpoint was the change in modified Rodnan skin score (mRSS) at week 24. Use of PVAC in patients with SSc appeared safe and was associated with a trend towards improved skin scores in the 15 microg treatment group

Urokinase therapy[16]

Gradual clinical improvement was observed with urokinase therapy, as evidenced by a noticeable restoration of skin elasticity and softness. Moreover, patients reported less intense symptoms of Raynaud's phenomenon and improvements in articular range, including previously limited movements. The authors concluded that 'therapy with urokinase seems to be a rational treatment in this disease' as it appears to 'modify the course and evolution of systemic sclerosis'.

CURRENT STUDIES, OPEN ENROLLMENTS

Allogeneic hematopoietic stem cell transplantation (NST) for patients with systemic sclerosis.[2-5]

This study is designed to examine whether treating patients with high-dose cyclophosphamide and fludarabine (drugs which reduce the function of the immune system) and CAMPATH-1H (a protein that kills the immune cells that are thought to be causing the disease), followed by return of blood stem cells that have been previously collected from the patient's brother or sister, will stop or reverse the disease.

ASTIS study[17]

High-dose immunoablation and hematopoietic stem cell transplantation versus monthly intravenous pulse therapy with cyclophosphomide in severe systemic sclerosis

This is a multicenter, prospective, controlled, randomized, phase III study comparing high-dose immunoablation and autologous hematopoietic stem cell transplantation with monthly pulse therapy with cyclophosphomide in patients with severe systemic sclerosis.

The European Group for Blood and Marrow Transplantation/ European League Against Rheumatism reported an analysis of their database of 57 patients with SSc treated by hematopoietic stem cell transplantation, with more than 6 months of follow-up. It revealed that the response in two thirds of the patients after hematopoietic stem cell

transplantation was durable, with an acceptable transplant-related mortality of 8.7%.[5]

Cyclophosphamide

(cyclophosphamide [50 mg/kg] intravenously daily for 4 consecutive days [total 200 mg/kg])

A placebo-controlled trial revealed that 1 year of oral cyclophosphamide in patients with symptomatic scleroderma-related interstitial lung disease had a significant but modest beneficial effect on lung function, dyspnea, thickening of the skin, and the health-related quality of life. The effects on lung function were maintained through the 24 months of the study.[18]

A further study revealed that after adjusting for the severity of fibrosis at baseline, CYC slowed the decline of lung volumes and improved dyspnea equally in the limited and the diffuse SSc groups. On the other hand, diffuse SSc patients responded better than limited patients with respect to improvements in skin thickening.[19] Though the results of cyclophosphamide therapy in improving lung function, skin scores, dyspnea, and health status–disability are established, except for a sustained impact on dyspnea, all of these effects waned and were no longer apparent at 24 months. Treatment strategies aimed at extending the positive therapeutic effects observed with cyclophosphamide should be considered.[20]

A potential combination, used with variation in India, is a combination with methyl prednisolone.[21]

Quinapril[22]

(Up to 80 mg/day in patients with limited cutaneous systemic sclerosis (lcSSc) for 3 years)

A multicentric trial, called the QUINS trial, has been initiated that includes, amongst other drugs, quinapril in scleroderma, which holds promise to replace the existing ACE inhibitor drugs in PSS.

Bosentan[5,23-25]

This appears to be beneficial for a variety of scleroderma symptoms, such as digital ulcers, pulmonary fibrosis, pulmonary hypertension, and skin fibrosis, as previously discussed.

SCOT clinical trial[26]

This is an ongoing trial which stands for 'scleroderma - cyclophosphamide or transplantation'; it will compare two potential therapies: autologous stem cell transplantation versus high-dose monthly cyclophosphamide.

Sildenafil[2,27] [Table 1]

Nitric oxide is an important mediator that has proinflammatory effects at high levels and is an important mediator of endothelium-dependent vasodilatation. The effects of nitric oxide are mediated via cGMP, and levels of this second messenger are increased when the degradative enzyme phosphodiesterase V is inhibited. This mechanism underlies the beneficial effect of agents such as sildenafil in the treatment of PAH complicating SSc.

Imatinib mesylate[2,28] [Table 1]

Pericytes may be important in the development of fibrosis by transdifferentiation into fibroblasts or myofibroblasts. This process may be intrinsic to wound healing and is regulated by platelet-derived growth factor. Its importance in organ-based fibrosis is unclear; but in the skin, recent studies have clearly shown that platelet-derived growth factor (PDGF) signaling is critical to pericyte activation and that this sequence occurs as SSc progresses. Imatinib also inhibits the activation of c-Abl, which is a key downstream molecule of transforming growth factor-beta signaling, and PDGF receptors.

Thus, imatinib effectively suppresses the activation and proliferation of fibroblasts, mesangial cells, and smooth muscle cells. Therefore, imatinib may overcome the limitation of current therapeutic strategy with corticosteroids and immunosuppressive agents for refractory diseases.

TRIALS COMPLETED: AWAITING RESULTS[1-4]

These include various studies which have finished but the results are formally awaited. They include oral type 1 collagen in scleroderma, persistent infection in systemic sclerosis, and psychological treatments for scleroderma.

Also, studies with some molecules like DMSO (dimethyl sulfoxide)[29] have been found to be inconclusive.

TRIALS COMPLETED: NEGATIVE RESULTS

The following treatments are either ineffective or unproven for the treatment of scleroderma. These range from the new molecules like anti-TGF-beta monoclonal antibodies (CAT 192),[5] relaxin[4,5], and the older drugs like azathioprine,[30] chlorambucil,[30] gamma interferon,[30] minocycline,[31] penicillamine[32-33] potaba[34] and tamoxifen.[35]

Penicillamine[32]

A conclusive study on this drug compared 822 mg daily versus low-dose 120 mg every other day. The study revealed that there was no statistical difference between either dose and the drug is no better than a placebo. But interest has been rekindled by a recent study[33] that retrospectively randomly selected 84 patients with diffuse cutaneous systemic sclerosis who had received D-penicillamine within 24 months of clinically detectable onset of skin sclerosis. At a median dose of 750 mg per day, statistically significant improvement with regard to skin, cardiac, pulmonary, and renal involvement was observed. The study concluded that in cases with diffuse cutaneous systemic sclerosis, with progressive disease of recent onset, D-penicillamine treatment at a median dose of 750 mg per day can cause a significant reduction in skin involvement and improvement with regard to renal, cardiac, and pulmonary functioning.

But as most of the literature on the drug is inconclusive[1-5] or has negative[32] results, the drug's role is still kept in this category.

THE FUTURE

Most of the latest research is now focused on pulmonary arterial hypertension (PAH), which is an important cause of death in systemic sclerosis (SSc), despite the improvement in therapies.[2-5,36]

Lately, new specific therapies have been developed targeting prostacyclin, endothelin, and nitric oxide pathways, the major pathogenic pathways leading to endothelial dysfunction in PAH.[2-4]

Epoprostenol improved life expectancy of patients with primary and secondary PAH. More stable analogues of prostacyclin, administrated by intravenous (iloprost, treprostinil), subcutaneous, inhalatory (treprostinil, iloprost), and oral route (Beraprost), have shown efficacy in PAH.[3,4,5,36]

Bosentan, the first oral endothelin receptor antagonist (with affinity for endothelin A and B receptors), improves exercise function and survival in PAH, both primary and secondary to autoimmune rheumatic diseases.[2-5,23-25] This is confirmed

Table 3A: A summary of known drugs used for systemic involvement[1-5,49-57]

Clinical condition	General advise	Specific advise
Raynaud's phenomenon and ischemia	avoid cold exposure, quit smoking biofeedback	**Vasodilator therapy** • Nifedipine 30-60 mg* • Amlodipine, 5-10 mg* • Felodipine, 5 to 10 mg * • Losartan 50 mg/d * • Sildenafil * • Prazocin • Iloprost * • Nacetylcysteine • Bosentan • Ketanserin (40 mg TID) • Fluoxetine, 20 mg/d • Pentoxifylline (400 mg TID) • Nitroglycerin paste **Surgical Therapy** (i) Stellate ganglion blockage (ii) Surgical cervical sympathectomy (iii) Digital sympathectomy
Finger / toe necrosis		i. Antibiotics ii. Intravenous (PGE1, PGI2) * (0.5 ng/kg bw per min) intravenous iloprost administration, for 6 hours daily over 21 days) iii. Atorvastatin 40 mg/day for 4 months iv. Sympathetic block v. Hydrocolloid membranes, over the noninfected ulcer. vi. Local nitroglycerin paste vii. Protect the finger. viii. Amputation

The response to any therapy for Raynaud's phenomenon is limited by the degree of existing structural narrowing of digital arteries. In patients with severe Raynaud's phenomenon and refractory digital ulcers, distal ulnar artery occlusion should be considered. *Therapy where evidence based study favour a therapeutic response

Table 3B: A summary of known drugs used for systemic involvement[1-5,49-57]

Clinical condition	General advise	Specific advise
Calcinosis		i. Intralesional steroids ii. Disodium etidronate iii. Warfarin
Skin		i. Hydration ii. Emollient iii. Retinoic acid iv. Steroids v. UVA vi. Autologous stem cell transplantation * vii. Cyclophoshamide *
Musculoskeletal Features		i. Nonsteroidal anti-inflammatory drugs ii. Physical therapy iii. Corticosteroid therapy
Gastrointestinal Reflux esophagitis	i. Elevation of head of bed ii. Small frequent meals iii. Avoid lying down within 3-4 hours of eating iv. Abstaining from caffeine v. Fatty foods and late-evening snacks should be avoided.	i. H2 blocker, ii. Proton-pump inhibitor iii. Metoclopramide (10 mg given 15-20 min before each meal up to 4 times a day). iv Erythromycin
Lower gastrointestinal disturbance		Broad-spectrum antibiotics(rotated every 2 weeks) ciprofloxacin, metronidazole, doxycycline, or erythromycin, Octreotide
Pulmonary Interstitial-fibrosis/Alveolitis		i. Corticosteroid * ii. Cyclophosphamide * iii. Azathioprine iv. Mycophenolate mofetil * v. Single-lung transplantation
Pulmonary-artery hypertension		i. Prostacyclin* a. Intravenous epoprostanol (2 ng/kg/min) b. Subcutaneous treprostinil (1.25 ng/kg/min) ii. Bosentan * 125 mg twice daily iii. Sildenafil iv. Inhaled nitric oxide Newer drugs i. Vasoactive intestinal polypeptide: inhaled VIP at daily doses of 200 mg in four single inhalations ii. Rho kinase inhibitors: fasudil, iii. Inhibitors of growth factor synthesis: imatinib & Adrenomedullin iv. Selective serotonin reuptake inhibitors (SSRIs) v. Hydroxymethylglutaryl-coenzyme-A reductase inhibitors
Pulmonary fibrosis		Not reversible, and therefore treatment is directed at symptoms or complications
Pulmonary infection		Requires prompt treatment with antibiotics
Cardiovascular system		i. Standard medical therapy for symptomatic pericarditis ii. NSAIDs / low dose steroids for myocarditis
Renal Involvement		i. High dose steroids ii. Angiotensin-converting enzyme inhibitors* iii. Dialysis. iv. Transplantation (not candidates for kidney transplantation because of the other systemic manifestations of SSc)

The response to any therapy for Raynaud's phenomenon is limited by the degree of existing structural narrowing of digital arteries. In patients with severe Raynaud's phenomenon and refractory digital ulcers, distal ulnar artery occlusion should be considered. *Therapy where evidence based study favour a therapeutic response

by new drugs like sitaxsentan and ambrisentan, selective endothelin A receptor antagonists.[3,5,36]

Inhibitors of NO degradation, such as sildenafil, a phosphodiesterase (PDE) type 5 inhibitor, improved functional and hemodynamic parameters without significant side effects.[3-5,27] Vardenafil and taladafil, longer-acting PDE inhibitors, also have vascular pulmonary selectivity.[3,5,36]

Table 4: A summary of interventions according to the mode of action used in scleroderma[1-5,42-47,49-58] with focus on drugs used for skin involvement*

General Measure*	Avoid use of detergent soaps .
	Apply hydrophilic ointments.
	Regular exercise for flexibility of extremities and pliability of skin.
	Topical retinoids
Antifibrotic therapy	Cyclophosphamide*
	PUVA/UVA1
	Colchicine
	Recombinant humán relaxin
	D-penicillamine
	Interferon-α
	Minocycline
	Methotrexate
	Cyclosporin
	Tacrolimus
	Relaxin
	IVIg
	Newer drugs
	• Recombinant human antitransforming growth factor-b1 antibodies :
	• CAT-192
	• Tyrosine kinase inhibitors :Imatinib mesylate
	• Histone deacetylase inhibitors :Trichostatin A
Immunsuppression/Antiinflammatory	Cyclophosphamide*
	Methotrexate*
	Mycophenolate mofetil*
	Stem cell transplantation*
	Cyclosporine
	Extracorporeal photopheresis
	5 FU
	Azathioprine
	Chlorambucil,
	PUVA/UVA1
Steroids ¥	Lung(alveolitis)
	CVS (myocarditis)

¥ Steroids *per se* have no role to play in the skin pathology of PSS,[1-5,49-51,54,55,58]and their use is at best in lung involvement.[52-53] No trial[1-5] has shown a sustainable positive effect, and thus steroid (pulse or oral) should be avoided except in specific systemic involvement. Glucocorticoids are not effective in improving or preventing skin induration and the progression of SSc.[54] Though occasional case reports claim reversal of disease[59] the overwhelming data,[1-5,49-51,54,55,58] is against the rampant use of steroids specially in view of side-effects reported [60.61,62]

a) Low-dose prednisone (10 mg/d or less) - edematous phase (skin involvement); joint and tendon pain.[54]

b) High-dose prednisone (20-30 mg/d) with steroid-sparing agent such as methotrexate or azathioprine - inflammatory myositis, pericarditis, early active alveolitis.[42,53,54]

c) Glucocorticoids have been associated with the development of renal crisis.[54]

d) Diffuse cutaneous SSc showed a significant association between *prior* high-dose glucocorticoids (prednisone 15 mg/d) and the development of scleroderma renal crisis.[54]

* Therapy where evidence based study favour a therapeutic response

All these drugs may be used in combination, to maximize their clinical benefit not only in patients unresponsive to single drugs but also potentially as initial therapy for PAH.

A recent review describes the role of natural therapies in scleroderma. It reviews several promising natural treatments for scleroderma, including para-aminobenzoic acid, vitamin E, vitamin D, evening primrose oil, estriol, N-acetylcysteine, bromelain, and an avocado/soybean extract.[37]

Most pharmacotherapeutic interventions to treat the disease remain empiric. Efforts to document efficacy have been disappointing when therapies are tested in controlled trials.[38-48] Many of these trials were doomed to fail, given the heterogeneous nature of disease expression; and too often, patients had late disease with established fibrosis that would not necessarily be amenable to the treatments tried.

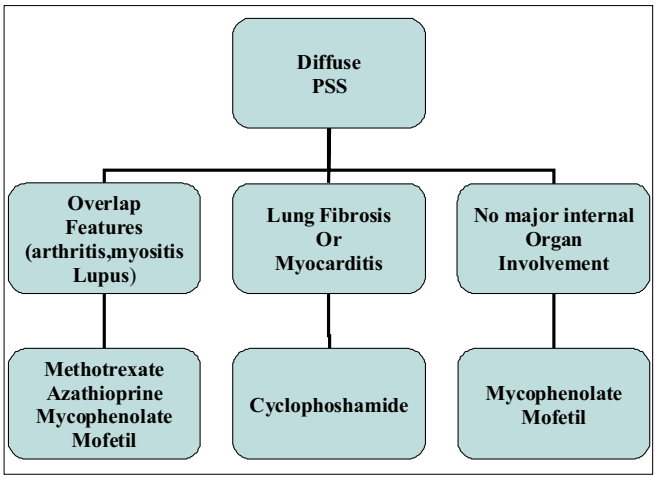

Figure 1: Therapeutic guideline based on present evidence based data in the management of PSS by the UK Study Group[55]

Clinical trials are characterized by their ability to answer very specific, straightforward questions in a well-defined relatively homogeneous patient population. Although this can provide important answers, it may not be representative of complex real-life scenarios. Other problems are that the patient populations tend to be highly selective, long-term outcome studies are notoriously difficult to perform, it is difficult to enroll adequate patient numbers, the disease is extremely slow to progress, and spontaneous improvement is observed in many. This makes it difficult to show benefits of therapy over placebo. As a result, meaningful results are more likely to be obtained by identifying and targeting patients who are most likely to progress, rather than those who remain stable over the course of a clinical trial.

The optimal way to achieve this is a matter of much debate; and till then, therapy will largely depend on symptomatic relief[49-51] hoping for the natural course of disease to supervene and lend a hand to the existing therapeutic regimens[51-61] [Tables 3, 4, Figure 1].

The best "disease modifying therapy "at present seem to be immunosuppressive drugs [Figure 1].

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