Therapeutic options for systemic sclerosis

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ABSTRACT

Systemic sclerosis is an uncommon connective tissue disorder characterized by vascular damage, immune cell activation and fibrogenesis. Each of these components may respond to different therapies. Therefore, a combination strategy treating all three processes is more likely to control the disease than single agent therapy. Clinical trials have gone a long way towards defining the therapy of scleroderma and many drugs previously used for scleroderma have been critically assessed. Angiotensin blockade is effective in treating as well as preventing scleroderma renal crisis. The 9-year cumulative survival has improved from 38% to 68% after the introduction of angiotensin blockade. There is definitive evidence supporting the use of cyclophosphamide in systemic sclerosis associated alveolitis. Newer molecules aimed at various cytokines are being tried. The therapy for systemic sclerosis is far from perfect at present. But, individualization of the treatment with respect to stage and subset of disease as well as organ involvement can eventually result in rational, effective management.

KEY WORDS: Scleroderma, Treatment, Systemic sclerosis

INTRODUCTION

Systemic sclerosis is an uncommon acquired connective tissue disorder characterized by an abnormal thickening of the skin. It is a multisystem disease with overproduction of collagen, widespread vascular damage with the development of microvascular obliteration, and tissue infiltration of mononuclear inflammatory cells. Though externally the skin seems to bear the brunt of the disease, internally various organs are equally affected by the same process.

TREATMENT CONCEPTS

The goals of treatment are:
1. Prevent internal organ damage.
2. Arrest or slow the deterioration of function in previously involved organs.
3. Improve the function of previously involved organs, including the skin.

The three underlying processes in systemic sclerosis are vascular damage, immune cell activation and fibrogenesis. Each of them may respond to different therapies (Figure 1). Therefore, a combination strategy treating all three processes is more likely to control the disease than single agent therapy. Since endotheliopathy and vasospasm are features throughout the course in diffuse scleroderma and limited scleroderma, vascular therapies should be used in combination with other agents. Moreover, therapies must also be matched to the disease stage and subset. Thus, for early diffuse systemic sclerosis, immunosuppressive treatment is the most appropriate...
approach. At later stages, antifibrotic interventions are most important. Vasodilator intervention is important at all stages of the disease.

**Status of established therapies for scleroderma**

Clinical trials have gone a long way towards defining the therapy of scleroderma and many drugs previously used for scleroderma have been critically assessed.

**D-Penicillamine**

This has been one of the most commonly used drugs in the management of systemic sclerosis due to its property of interfering with the cross linking of collagen, thus increasing the soluble collagen, and a probable immunomodulatory effect. Since 1966, many studies have tried to assess its efficacy, but they have been uncontrolled, have used different dosages and durations, and have showed a wide spectrum of conclusions, varying from no effect to 70% favorable response. In 1982, Steen et al analyzed a large group of patients with early diffuse scleroderma. In this retrospective study, D-penicillamine treatment was associated with significant improvement in the skin thickness, better survival and fewer instances of scleroderma renal crisis compared with a similar (non-randomized) comparison group receiving no treatment or other treatments. Twice as many patients had more than 25% improvement in skin score. New organ involvement was reduced and the 5-year cumulative survival rate was also higher in the penicillamine group. The drawback of this trial is that it did not have any randomized comparison group. Recently a large, randomized, double blind, multicenter study of D-penicillamine was conducted to compare low dose (62.5 mg daily) with high (conventional) dose (750 mg daily) therapy in patients with early diffuse systemic sclerosis (disease duration < 20 months). It was expected that the conventional dose would be more effective than the low dose, but the skin scores in both the groups improved significantly and no dose response was observed. No difference was found in the mortality or the incidence of renal crisis in the two groups. This trial suggests that treatment with low doses of D-penicillamine is as effective as that with high doses, but it suffers from the disadvantage of not including controls. Thus conclusive data about the efficacy of D-penicillamine are still lacking.

**Methotrexate**

Using a logical, but complex, definition of improvement, a trial showed a 63% improvement in 15 patients who were treated with methotrexate compared with a 10% improvement in 12 patients who were treated with placebo (p<0.05). The study examined 29 patients with an average disease duration of 38 months. Another trial examined 71 patients who had diffuse scleroderma (median disease duration of 7 months). The modified Rodnan skin score (MRSS) improved by 4.1 units in the patients who took methotrexate but worsened by 1.8 units in patients who took placebo (p<0.009). The UCLA skin score, which measures tethering, reached statistical significance (p<0.05). This trial showed trends to response without reaching statistical significance. Thus,
the exact role of methotrexate as a disease-modifying agent in systemic sclerosis remains uncertain.

Vasodilators
Two groups of vasodilators are available for use in scleroderma: calcium channel blockers and angiotensin converting enzyme (ACE) inhibitors (enalapril)/angiotensin receptor blockers (losartan). Both have an evidence-based benefit. However, when compared, nifedipine, a pure vasodilator, was less effective or of no benefit in Raynaud’s phenomenon. A comparison of nifedipine vs. losartan also showed statistically better results with losartan. Thus angiotensin converting enzyme inhibitors/angiotensin receptor blockers are more effective.

Effects of angiotensin blockade: Angiotensin II is a profibrotic agent and induces collagen and fibronectin synthesis. It also stimulates transforming growth factor-beta (TGF-β) gene expression in fibroblasts and endothelial cells. Angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) block the pro-fibrotic renin angiotensin axis. Losartan also reduces the lung fibroblast proliferation and collagen production induction by angiotensin II in vitro. Preliminary evidence also suggests that losartan not only improves Raynaud’s phenomenon but also beneficially modulates the levels of pro-collagen peptides and circulating isoforms of cell surface adhesion molecules. Angiotensin-converting enzyme is also involved in the degradation of bradykinin, thereby regulating its effects on fibrinolysis and on platelet activation and aggregation. Bradykinin, a potent vasodilator, reduces the production of tissue plasminogen activator and stimulates endothelial receptors that trigger prostacyclin and nitric oxide release. ACEIs/ARBs are thus likely to have disease-modifying properties in addition to a vasodilator property, as is commonly believed. ACEIs reverse the scleroderma renal crisis. Retrospective studies already show that the 9-year cumulative survival has improved from 38% to 68% after the introduction of ACEIs in the management of scleroderma. Thus, there is abundant evidence about the utility of ACEIs in scleroderma and the introduction of this group of drugs has resulted in a significant reduction in the mortality due to the disease.

Corticosteroids
Corticosteroids are indicated only in inflammatory myositis, the edematous phase of systemic sclerosis and for interstitial lung disease secondary to systemic sclerosis on a short term basis. The dosage of prednisolone used is 15-20 mg to avoid the long-term complications of steroids. One potential complication is their association with scleroderma renal crisis. High doses (prednisolone > 30 mg) have been proved to be a factor associated with the development of renal crisis.

Pulse corticosteroids
Indian studies have shown the usefulness of pulse corticosteroid therapy in systemic sclerosis. An improvement in skin thickness, episodes of Raynaud’s phenomenon, pulmonary function, and calcinosis has been shown with pulse steroids (100 mg dexamethasone in 5% dextrose given intravenously for 3 days per pulse). In one study, the histopathological changes (perivascular mononuclear infiltrate, vessel wall changes, papillary dermis homogenization, and reticular dermis hyalinization) were evaluated in 8 patients with scleroderma on pulse dexamethasone. Although induration improved clinically, there was no consistent or uniform improvement in the various histopathological parameters. Pulse steroid therapy in other dermatological diseases has been shown to be free of the common side effects of long term steroid therapy. The question of pulse corticosteroid-induced osteoporosis remains unanswered as the trials looking for osteoporosis are limited to one or two pulses only. However, role of pulse steroids remains questionable in view of reports regarding the causation of renal crisis with long-term high dose steroids.

Cyclophosphamide
Cyclophosphamide has been used for patients with interstitial lung disease. Three trials have shown improvement in lung function with cyclophosphamide as compared to prednisone or D-penicillamine. The largest series with 103 patients followed up over 13 months showed a median survival of 89% in those treated with cyclophosphamide compared to the 71% in the untreated group. Thus there is definitive evidence supporting the use of cyclophosphamide in systemic sclerosis associated alveolitis and
cyclophosphamide pulse therapy is regularly used for this indication in systemic sclerosis.

**Infliximab**
Infliximab has been recently tried in scleroderma. It was combined with methotrexate in a patient with CREST syndrome and refractory ulcers with effective healing of the ulcers.  

**Minocycline**
A recent study involved subjects with diffuse systemic sclerosis of less than 5 years duration who were treated with minocycline at a dose of 50 mg bid for one month followed by 100 mg bid for up to a year. Mean skin score improved only modestly in this study, the small degree of improvement (mean change in MRSS = -3.9 or 12.6%) was similar to that expected in the natural course of this disease. Minocycline has also not been found to alter the metabolism of collagen 1 by dermal fibroblasts. However, it may be useful in calcinosis associated with scleroderma.

**Thalidomide**
Thalidomide is a partial inhibitor of TNF-a production by LPS stimulated monocytes both in vitro and in vivo. Thalidomide seems to stimulate a Th-1 type of response. The use of Thalidomide has been directed at the immunological component of scleroderma. A striking effect has been seen on extremity ulcers in scleroderma patients. Post treatment skin biopsies showed loosening of the collagen bundles and decrease in the thickness of the epidermal layer. Improvement was also seen in other symptoms like GE reflux but not in Raynaud’s episodes.

Figure 2 shows a simplified protocol for the management of systemic sclerosis.

**ORGAN BASED THERAPIES**
Effective management of systemic sclerosis consists of early detection of specific organ based complications. Specific organ based strategies are:

**Management of critical digital ischemia**
Digit threatening ischemia is characterized by severe pain and ischemic demarcation of the digit. Vasodilator therapy is maximized. For rapidly advancing ischemic lesion, anticoagulation with heparin is initiated. Low

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**Systemic sclerosis treatment decision making**

1) Subset  
2) Stage  
3) Autoantibody profile

Immunosuppressive therapy  
Vasodilator therapy  
Antifibrotic therapy

Risk stratification  
Organ based screening for involvement

GERD  
Proton pump inhibitors

Midgut disease  
Antibiotics

ILD  
Azathioprine  
Cyclophosphamide

Renal involvement  
ACE inhibitors

Pulmonary hypertension  
Iloprost, warfarin

**Figure 2: Protocol for the management of systemic sclerosis**
Key: GERD: Gastro Esophageal Reflux Disease, ILD: Interstitial Lung Disease
molecular weight dextran and pentoxiphylline infusion have been tried with variable success. Prostacyclines have been a promising drug in this regard. Epoprostenol, 0.5 to 2 ng/kg/min continuous infusion for 1 to 3 days or iloprost infusion at doses of 0.5 to 2.0 ng/kg/min can be administered daily for 1 to 3 days. When medical treatment fails, surgical interventions may be appropriate.

Renal crisis
It is one of the major complications of systemic sclerosis. Corticosteroid use (>30 mg prednisolone per day) may predispose to renal crisis. Early use of ACE inhibitors, along with other improvements in managing renal crisis, has significantly reduced the mortality.

Interstitial lung disease
Currently there is no consensus on the exact treatment for lung fibrosis. As stated earlier some trials have suggested benefit from the use of cyclophosphamide.

Pulmonary hypertension
This is one of the most lethal complications. It can occur with established interstitial lung disease (secondary pulmonary hypertension) or without it (isolated pulmonary hypertension). The latter is associated with limited scleroderma. The use of prostacyclin analogues has been a major advance in the management of isolated pulmonary hypertension. The other drugs used are warfarin and calcium channel blockers. Newer agents under trial are inhaled iloprost, nitric oxide, oral or inhaled prostacyclin formulations, and oral endothelium receptor antagonists such as bosentan. Bosentan (for the pulmonary hypertension of scleroderma), cyclophosphamide (for scleroderma alveolitis) may improve organ function or functional activities, whether they are truly disease-modifying remains to be proven.

Skin sclerosis
UVA phototherapy
Collagenase activity has been shown to be decreased in scleroderma fibroblasts and UVA has been tried for its collagenase inducing activity. Though the exact mechanism for this is not known, singlet oxygen has been proposed as one of the factors. Low dose, medium dose as well as high dose UVA, have been shown to improve skin lesions clinically as well as histopathologically in patients with localized and systemic sclerosis.

PUVA for scleroderma
PUVA bath photochemotherapy has been tried in an effort to avoid the side effects of oral administration and found to be useful. Oral psoralens with UVA have been tried but with limited success.

Targeted molecular therapy
This has been the result of a better understanding of immunologically triggered fibrosis. Candidate molecular targets for therapeutic modulation in systemic sclerosis are listed in Table 1.

SUPPORTIVE TREATMENT
Gastrointestinal reflux
Reflux can be taken care of by small frequent meals, elevating the head end of the bed, avoiding tea, coffee, alcohol and chocolate and with the use of prokinetic agents (domperidone, cisapride 10-20 mg tds, and

<table>
<thead>
<tr>
<th>Molecular target</th>
<th>Effects</th>
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<tbody>
<tr>
<td>Cytokines</td>
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<tr>
<td>Interleukin-4</td>
<td>Beneficial effect in tight skin mouse model</td>
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<tr>
<td>Interleukin-6</td>
<td>Anti IL-6 blocks the pro-fibrotic activity of scleroderma conditioned medium</td>
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<tr>
<td>β-Fibroblast growth factor</td>
<td>Endothelial cell induced activation of fibroblasts blocked by anti-βFGF</td>
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<tr>
<td>Transforming growth factor-β</td>
<td>Antibody to TGF-β reverses skin fibrosis in the minimal mismatch GVH disease murine model of scleroderma</td>
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<td>Adhesion molecules</td>
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<tr>
<td>Intercellular adhesion molecule-1</td>
<td>Enhanced lymphocyte-fibroblast interaction for scleroderma cells in vitro blocked by anti-ICAM-1</td>
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<tr>
<td>Intracellular signaling</td>
<td></td>
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<tr>
<td>Inhibitor of geranylgeranyl transferase</td>
<td>Specifically downregulates extracellular matrix genes in scleroderma fibroblasts</td>
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Table 1: Candidate molecular targets for therapeutic modulation in systemic sclerosis
mozapride 5 mg tds). Cisapride and mozapride score over domperidone because they are devoid of anti-
dopamine effects. Blood levels of cisapride are
increased due to inhibition of CYP3A4 by erythromycin,
ketoconazole and can cause arrhythmias. Mozapride
does not cause this side effect.

Malabsorption
Management of secondary malabsorption requires
antibiotics, such as tetracycline or doxycycline.

Raynaud’s phenomenon
The number of episodes of Raynaud’s phenomenon can
be decreased by warm dressing, avoiding smoking, beta
blockers, methysergide, and amphetamines. Apart from
calcium channel blockers and ACE inhibitors, oral 5-
HT blockers, local nitroglycerine paste, and sympathectomy are also useful.

Arthralgias and arthritis
These can be managed by using NSAIDs, e.g.
indomethacin 25 mg tds.

Deformities
To prevent any deformities it is important to start
physiotherapy right from the beginning.

Calcinosis
Calcinosis is one of the common manifestations of
scleroderma especially of the CREST syndrome. It is
seen mainly in the hands around the joints and can
form sterile abscesses and small ulcers that can get
infected. Saline compresses can reduce the pain and
swelling until the calcium is extruded. The calcium mass
may be excised. Colchicine reduces the local inflam-
mation due to the calcium and promotes healing.

Cutaneous ulcers
Cutaneous ulcers can be protected with an occlusive
dressing. Ischemic digital tip ulcers may be protected
with a small plastic “cage.”

Adequate skin lubrication is difficult to maintain.
Patients should bathe less and use moisturizers. A daily
physical therapy program emphasizing a full range of
motion of all large joints is important.

EXPERIMENTAL DRUGS

Recombinant human relaxin
Normally present in significant amounts in pregnant
women, relaxin has been shown to reduce synthesis of
type 1 collagen by scleroderma fibroblasts. A dose
escalating, placebo controlled trial showed benefit
based on self-reported health assessment questionnaire
and skin score.

Oral tolerization to type 1 collagen
This therapy is based on the rationale that oral
tolerance to type 1 collagen can be induced, and the
hypothesis that an autoimmune reaction to native
collagen may contribute to the pathogenesis. Oral
collagen is apparently safe and may also be useful in
established disease, which is otherwise difficult to treat.

Anti-thymocyte globulin (ATG)
ATG is used as a treatment for scleroderma because of
its efficacy as an immunosuppressive agent. There have
been several encouraging case reports of the use of
ATG. A trial in patients with early (less than 3 years
duration) diffuse scleroderma confirmed its feasibility
and tolerability, but the endpoint changes were
disappointing.

Immonoablation with autologous peripheral stem

cell rescue
If scleroderma is driven by an autoimmune process,
ablation of self-reactive lymphocyte clones may block
pathogenesis. Pilot trials to evaluate this treatment are
underway in USA.

Finally, here is a checklist for the treatment of systemic
sclerosis:
• What every patient of systemic sclerosis should be receiving:
  o Aspirin (150 mg/day)
  o ACE inhibitors or angiotensin receptor blockers
    (enalapril 2.5-10 mg OD, losartan –25-50 mg OD)
  o A calcium channel blocker can be added
    (nifedipine 5-20 mg tds)
  o Organ specific therapy such as a proton pump
    blocker (omeprazole 20-40 mg OD) for esoph-
ageal reflux apart from the non-pharmacological
Other treatment would depend on the specific organ involvement e.g. interstitial lung disease: cyclophosphamide.

MONITORING DISEASE ACTIVITY

- Skin thickness scores: The most widely accepted method for monitoring skin changes in systemic sclerosis is by simple clinical palpation. The modified Rodnan skin score employs a qualitative rating scale (0, normal skin; 1, mild; 2, moderate; 3, severe thickening) of the findings on clinical palpation of 17 body areas and thus is a semi-quantitative tool for clinical research as well as a measure of clinical progress in the individual patient.\(^9\)

- Health assessment questionnaire (HAQ–Disability Index (DI) has been shown to be the most accurate predictor of survival; it outperformed a variety of clinical and laboratory features, including evidence of internal organ involvement in a longitudinal study of 1250 patients with 5.2 years follow up.\(^9\) DI score correlates well with total skin thickness score, reduced fist closure, and proximal muscle weakness.\(^9\)

- The frequency of episodes of Raynaud's phenomenon and the presence as well as development of new subungual ulcers are markers of disease activity.

- Internal organ involvement and deterioration or improvement in the same on follow up.

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