Chapter 100
Scleroderma: From Therapeutic Nihilism to Therapeutic Optimism

INTRODUCTION
Scleroderma or systemic sclerosis (SSc) is a systemic disorder that is characterized by excessive collagen deposition, autoimmunity and extensive vascular damage that involves multiple organ systems.

The therapeutic management of scleroderma was very frustrating, but in recent years introduction of few new drugs have changed the picture from “nothing to offer” to “many things to offer”.

The rational treatment of SSc should be based on a hypothesis of its pathogenesis, first proposed by Furst (Flow chart 1).

DRUGS THAT PREVENT VASCULAR DAMAGE
Vascular involvement is often seen in the early stages of SSc. An activated immune system and certain external stimuli, such as cold and trauma, can lead to activation of endothelial cells, which is followed by endothelial damage.

Epoprostenol: Synthetic Prostacyclin Analog
Prostacycline is a product of arachidonic acid in the vasculature and is produced mainly by the endothelial cells. Epoprostenol is given as a continuous intravenous infusion using a portable infusion pump that is connected by a tunnelized central venous catheter.

Treprostinil
Treprostinil is a newer prostacycline analog and is more stable than epoprostenol at room temperature with a longer half-life. Another advantage of treprostinil is that it may be administered as subcutaneous infusion rather than intravenous infusion.

Bosentan
Bosentan is an oral endothelin antagonist, which blocks endothelin-1 receptors A and B. Endothelin-1 is a potent endogenous vasoconstrictor and smooth muscle mitogen. A randomized placebo controlled study by Channick et al. was conducted on 32 patients who had severe primary pulmonary hypertension or scleroderma-related pulmonary hypertension in five centers.

Angiotensin-Converting-Enzyme Inhibitors
Scleroderma renal crisis (SRC) was the leading cause of death in SSc before angiotensin-converting-enzyme inhibitors (ACEI) were widely used. A prospective study by Thurm and Alexander in 1984 documented that 87% patients who had SRC responded to captopril. Based on the prospective cohort data, Steen et al. had suggested that ACEI should be started as soon as renal crisis is diagnosed.

SUPPRESSION OF AUTOIMMUNITY AND INFLAMMATION
Several types of inflammatory cells infiltrate the affected tissue. Different subsets of “T” lymphocyte may be observed in different affected organs in various stages of SSc. CD4 lymphocytes are increased in the affected skin, whereas CD8 lymphocytes are found more commonly in bronchoalveolar lavage of patients who have scleroderma-related interstitial lung disease (ILD). Several autoantibodies including anti-topoisomerase 1 (Sc170) antibodies and anticientromere antibodies are detectable in scleroderma patients.

Cyclophosphamide
Most of the studies that were done with cyclophosphamide were aimed at improving pulmonary function. One early example is the open trial by Silver et al. They showed that in patients who had alveolitis, a mean daily usage of 100 mg of cyclophosphamide in addition to low-dose prednisone, resulted in an improvement in pulmonary function 6 months after treatment. Patients of SSc with ILD treated with oral cyclophosphamide showed statistically
significant improvement in forced vital capacity (FVC) than placebo in scleroderma lung study (SLS).\textsuperscript{6}

**Mycophenolate Mofetil**

Like cyclophosphamide, mycophenolate mofetil has also immunosuppressive effects, and in SLS II, this drug is being compared with cyclophosphamide and placebo. The result of this large trial is awaited.\textsuperscript{7}

**Methotrexate**

Several studies were performed that used methotrexate to treat SSc and used skin scores as primary outcome. Two major randomized control trials had been conducted. Vander Hoogan et al. completed a small 12 months study.\textsuperscript{8} The first 6 months they compared methotrexate and placebo using a logical but complex definition of improvement. This 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.

**Chlorambucil**

Chlorambucil is an alkylating agent with immunosuppressive effects. The rationale for using chlorambucil is supported by the presence of T cells in skin biopsy and abnormalities of T-suppressor and T-helper lymphocyte ratio and function.

**5-Fluorouracil**

Cases et al. performed a randomized double-blind, placebo controlled international collaborative study in 1990 for the treatment of SSc.\textsuperscript{9} Although this trial only had 20 patients enrolled in each group, the result was encouraging.

**Stem Cell Transplant**

Stem cell transplant (SCT) that uses high-dose cyclo-phosphamide (120–200 mg/kg) plus antithymocyte globulin with or without total body radiation was done in more than 60 patients who had the most severe progressive form of SSc. In a European trial, SCT showed some response in 69%, worsening in 7% and 17% transplant-related mortality.\textsuperscript{10} Stem cell transplant of course represents extremely aggressive and effective immunosuppressive therapy. Now, three randomized control trials: (1) American Systemic Sclerosis Immune Suppression versus Transplant (ASSIST); (2) Autologous Stem Cell Transplantation International Scleroderma (ASTIS) and (3) Scleroderma Cyclophosphamide versus Transplant (SCOT) are evaluating the role of hematopoietic SCT in SSc.\textsuperscript{11,12}

**Future Therapy**

Mekown et al. have taken a different approach.\textsuperscript{13} Bovine type I collagen, given orally, is being used as a toleragen in an attempt to induce specific down regulation of the immune response.

**AGENTS TO INHIBIT FIBROSIS**

Excessive collagen deposition is the hallmark of the SSc. When activation and proliferation of fibroblasts occurs, increased collagen may be produced and deposited in the extracellular matrix.

**Gamma Interferon**

Interferon gamma, which is produced by activated T-cells, activates macrophages and is a potent inhibitor of collagen synthesis.

**Alpha Interferon**

Interferon alpha has also been tried in SSc, but trial results are disappointing.

**D-Penicillamine**

A large randomized, double-blind multicenter study of D-penicillamine compared low-dose D-penicillamine 62.5 mg daily with high-dose D-penicillamine 750 mg daily.\textsuperscript{14} This trial examined patients who had early diffuse SSc. There were no differences found in skin score, mortality or incidence of renal crisis.

**Relaxin**

Relaxin is a protein that is secreted by corpus luteum and placenta during pregnancy, and may have a role in loosening of pelvic structures in the preparation for delivery by enhancing collagen degradation and inhibiting collagen synthesis.

**FUTURE THERAPY**

With increased understanding of the pathogenesis of SSc, new therapeutic targets are being studied.

Transforming growth factor \(\beta\) (TGF-\(\beta\)) is a pleiotropic cytokine with vital homeostatic functions. Aberrant TGF-\(\beta\) expression is implicated in the pathogenesis of fibrosis in SSc. So there is an increasing interest in developing anti TGF-\(\beta\) compounds. In normal adult fibroblasts, TGF-\(\beta\) induces the expression of connective tissue growth factor (CTGF). Moreover CTGF independently promotes fibroblast proliferation and matrix deposition. Thus, TGF-\(\beta\) and CTGF both can be molecular therapeutic target in this disease. An anti TGF-\(\beta\)-1 human recombinant antibody has been tried in randomized controlled trial, but it failed to show any statistically significant improvement.\textsuperscript{15}

Imatinib mesylate can act as an antiinflammatory agent in SSc by inhibiting platelet derived growth factor and TGF-\(\beta\). The TGF-\(\beta\)-signal transduction pathway involves transmembrane serine threonine kinase that phosphorylates a group of intracellular signaling proteins called SMADs. Imatinib mesylate blocked activation of the Smad1 pathway in TGF-\(\beta\) stimulated control fibroblasts and reversed activation of this pathway in SSc fibroblasts. Likewise, blockade of c-Abl abrogated activation of the Smad1 pathway in SSc fibroblasts.\textsuperscript{16}

In a study by Varga J et al., some improvement in ILD and skin fibrosis was observed in SSc patients but they did suffer from adverse effects of imatinib (Figure 1).\textsuperscript{17}

Anti TNF-\(\alpha\) antibody treatment is now, approved in various autoimmune diseases and it has also been tried in SSc. Among all the agents, infliximab and etanercept showed some improvement in SSc patients but it was not statistically significant.\textsuperscript{19}

**Dimethyl sulfoxide (DMSO)**, a substance that is said to solubilize collagen, was tested in 84 patients who had scleroderma-related skin disease for its ability to reduce digital ulcer pain and promote ulcer healing, using 0.85% normal saline, 2% DMSO and 70% DMSO.\textsuperscript{20} Although pain was improved in a subset of patients, there were no statistically significant changes found in other parameters.

Cyclofenil is diphenyl ethylene derivative that is related to stilboestrol. It is also a weak estrogen and may interfere with connective tissue metabolism.

**Potassium aminobenzoate (KPA)** was reported to be associated with skin softening from a retrospective study of 224 patients who had scleroderma by Zarafonetis et al.\textsuperscript{21} A multicenter randomized, double-blind placebo controlled trial was later conducted by Clegg et al.,\textsuperscript{22} but after a 48 weeks follow-up, there was no change in skin score.

**Ketotifen** is an oral mast cell stabilizing agent, which may inhibit the release of inflammatory mediators and possibly prevent activation of fibroblasts. After the 6 months trial period of 3 mg of ketotifen twice daily versus placebo, there was improvement in pruritus but no significant change in total skin score, lung function or global assessment.\textsuperscript{23}
SUMMARY

Treatment of SSc has been somewhat haphazard and treatment has often been “borrowed” from the experience gained from treating other connective tissue diseases. There was a period of time that was focused mainly on organ-specific manifestation of SSc and some advances in preventing vital organ damage was achieved. The vast improvement of mortality from the use of ACEI raises one’s hope for other effective therapeutic interventions. At this junction, the evidence is strong that the ACEIs that are used in SRC are disease modifying even without proving it by a randomized control trial.

There are suggestions that Bosentan (pulmonary hypertension of scleroderma), cyclophosphamide (SSc alveolitis), SCT, interferon-gamma (interstitial fibrosis) and methotrexate (skin thickening of diffuse scleroderma) may improve organ function or functional activities, but whether they are truly disease modifying remains to be proven.

So, in conclusion we can say with reasonable grounds that a number of drugs are in the pipeline to prevent organ damage in SSc… sunny days with therapeutic optimism is definitely waiting for us!!

REFERENCES


