The Scleroderma Education Project™

Systemic Sclerosis Disease Staging and Treatment Overview

Introduction

In 1979, a research paper [1] titled "Endothelial Injury in Scleroderma" included the following passage:

"Many theories exist regarding the etiology and pathogenesis of scleroderma: endocrine dysfunction, nervous disorder, infection, physical trauma of various types, and immune factors. Many, if not all, of the manifestations of scleroderma can be explained on the basis of functional and structural vascular compromise after repeated vascular insults, subsequent healing of vascular walls with proliferative vascular response, and luminal narrowing. The coagulation cascade may be triggered by the intimal lesion, leading to fibrin deposition, reduced blood flow, and local ischemia."

Basically, what this is saying is that while we don't know exactly what triggers scleroderma, all symptoms that ultimately arise may be the result of a chain of events that starts as a result of repeated damage to the cells that line the smallest blood vessels (endothelial layer on the inside of microcapillaries). While this endothelial damage model is now commonly accepted by most scleroderma researchers, many theories have been floated about the specific mechanisms of that damage, usually centered around various biological processes and cellular level interactions.

Based on this theory, we propose that a simplified model for scleroderma symptom development and progression can be divided into five stages, as shown below.

Disease Staging

Stage	Description	Treatment Approaches

1	**Immune System Malfunction**
	Something triggers changes to the immune system that leads to the development of scleroderma-related pathogenic molecules (e.g., auto-antibodies) in genetically susceptible individuals. Possible triggers include environmental toxins such as silica dust or organic solvents, or infectious processes triggered by mycoplasma or other bacterial/viral organisms.
		• Hematopoietic Stem Cell Transplants (HSCT)
		• Immune system regulation
		  ○ Plaquenil
		  ○ IVIG
		  ○ Extracorporeal photopheresis

2	**Circulating Pathogenic Factors** The altered immune system generates destructive autoantibodies or other pathogenic molecules on an ongoing basis.	• Immunosuppressants, general or targeted, for example: o Prednisone o Methotrexate o Mycophenolate mofetil (Cellcept) o Cyclophosphamide (Cytoxan) o Rituximab (Rituxan)
3	**Microvascular Endothelial Damage** Autoantibodies or other circulating pathogenic factor either directly or indirectly cause repeated trauma to the endothelial layers of the microcapillaries.	• Therapeutic plasma exchange (TPE) may reduce or prevent endothelial damage and the later fibrotic disease stages.
4	**Fibrosis** Repeated trauma to the endothelium triggers a cascade of cellular level events that starts the fibrosis process.	• Anti-fibrotic drugs (currently in early testing stages): o Pirfenidone (Esbriet) o Imatinib mesylate (Gleevec) o Connective tissue growth factor inhibitors (CCG-203971)
5	**Organ Damage** The fibrosis eventually affects multiple organ systems, including the skin and internal organs.	• Targeted treatments, *e.g.* o Raynaud's/digital ulcers: ▪ Calcium channel blockers (nifedipine) ▪ PDE5 inhibitors (sildenafil) ▪ Dual endothelin receptor antagonists (bosentan) o GERD: oemeprazole, lansoprazole o Gastroparesis: metoclopramide o Scleroderma Renal Crisis: ACE inhibitors

Current Treatment Overview

Current systemic treatments for scleroderma are mostly focused on Stage 2 of the disease process. The logic is simple – suppressing the production of the presumably destructive pathogenic factors using immunosuppressive drugs should help to control the damage by reducing the number of circulating autoantibodies. While research indicates that immunosuppressive treatments may result in modest systemic improvement, any benefit stops when treatment stops, and symptoms then resume "normally." And, since most immunosuppressive treatments are potentially very toxic, the stronger immunosuppressive drugs can only be used for a relatively short time period. With any use of immunosuppressive drugs, there is also a significantly increased risk of long-term issues, such as greater risk of infections and cancer. A recent (2012) study [2] indicates that there has been no improvement

in overall survival rates for patients diagnosed with SSc in the past 40 years beyond what would be expected from overall improvements in longevity in the general population during this same time period. This suggests that any up-front improvements from the use of immunosuppressants are counter-balanced by long-term complications from this treatment approach.

A number of researchers are now focusing on Stage 4 of the disease process - reducing or preventing fibrosis and subsequent organ damage. An example of this is early stage research that is being done at Michigan State University [3]. Treatments that can reduce or prevent fibrosis can potentially be very helpful, but at this point it is too early to know whether these treatments will be safe enough to be used on a long-term basis without causing other systemic problems. Since this type of intervention is relatively late in the disease process, any treatment that can prevent or reduce fibrosis will need to be continued on a permanent basis. Because of this, safety will be a major consideration in whether or not drugs developed to deal with the fibrosis stage of scleroderma will be useful over the long run.

Once symptoms are clearly established, treatment focus usually switches to individual symptom management (Stage 5) even as general immunosuppressant treatments may be continued. There are a number of treatments for specific symptoms that are reasonably effective, at least initially. Standard treatments for various symptoms that occur frequently in scleroderma patients are covered in detail in the Scleroderma FAQ.

Our research focuses on Stage 3 of the disease process - damage to the endothelium - and how to prevent or reduce it. Our hypothesis is that interrupting this early stage of the disease process and preventing or reducing endothelial damage will lead to new treatment approaches that are likely to have a much greater potential for preventing or significantly delaying symptom progression than current treatment approaches focused on Stage 2 or Stage 4 of the disease process.

References

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2. Elhai M, Meune C, Avouac J, Kahan A, Allanore Y. Trends in mortality in patients with systemic sclerosis over 40 years: a systematic review and meta-analysis of cohort studies. *Rheumatology (Oxford)*. 2012;51(6):1017-1026. doi:10.1093/rheumatology/ker269.
3. Haak AJ, Tsou P-S, Amin MA, et al. Targeting the myofibroblast genetic switch: inhibitors of myocardin-related transcription factor/serum response factor-regulated gene transcription prevent fibrosis in a murine model of skin injury. *J Pharmacol Exp Ther*. 2014;349(3):480-486. doi:10.1124/jpet.114.213520.