The Annual Review: Systemic Sclerosis Research

A Clinical and Experimental Rheumatology review offers a critical analysis of recent studies on systemic sclerosis to best classify and manage this chronic condition.

There have been many developments in the treatment of systemic sclerosis throughout the last year. Researchers continue to explore the possibility of genetic influences in disease progression and the role of SSc antibodies for diagnosis. New criteria has been proposed for Very Early Disease Onset Systemic Sclerosis. These and other developments have led to improvements in disease control and a better quality of life for patients who live with systemic sclerosis, also known as systemic scleroderma.

In an annual overview of advances in the pathogenesis, diagnosis, classification and treatment of systemic sclerosis, Simone Barsotti, MD, of the University of Pisa in Italy, and colleagues, summarize and assess the scientific literature on systemic sclerosis published between January 2014 and July 2015 and available through Medline. Their report appears in the Aug. 5 online issue of *Clinical and Experimental Rheumatology*.

The following is a summary of the review, which was divided into nine sub-categories as follows:

**Classifying Systemic Sclerosis**

The criteria for systemic sclerosis established in 2013 by the American College of Rheumatology/European League Against Rheumatism are more sensitive and as result, more patients have been classified as having SSc. The classification criteria are more sensitive for subjects without patent skin involvement, but are less sensitive because of the removal of sclerodactyly and puffy fingers. Suggested modifications would classify subjects as having sub-clinical disease.

To overcome the issue of properly classifying subjects with sub-clinical disease, Very Early Disease Onset Systemic Sclerosis (VEDOSS) criteria have been proposed.

**The Pathogenesis of Systemic Sclerosis**

Although systemic sclerosis is not an inherited disease, genetic influences have long been suspected to impact the disease.

 Several studies reported that major histocompatibility complex (MHC) class II is the most significant in the development of the disease; however some studies reported other non-HLA genes that are associated with SSc susceptibility.
The most significant genes are in major histocompatibility complex (MHC) class II, but there are other genes, including those on the interferon-12 pathway. The search goes on for the trigger, perhaps human cytomegalovirus or parvovirus B19. Traffic pollution, such as diesel exhaust nanoparticles, may play a role. A mouse deficient in unkinase-type plasminogen activator may be a useful animal model. Vascular injury may lead to fibrosis, and several growth factors may mediate it. Or, intestinal microbiota may work in combination with IL-17.

Histologically, endothelial cell damage is accompanied by perivascular leukocyte infiltrates. Chemokines are upregulated. Autoantibodies to angiotensin II receptor type 1 and endothelin receptor type A have been implicated. Candidate genes are being studied for the deposition of extracellular matrix, including type I collagen. The causes of pulmonary artery hypertension are under study. Bone morphogenic protein receptor II, associated with inherited pulmonary artery hypertension, may give insight into the non-heritable types.

The Clinical Manifestations of Systemic Sclerosis

SSc antibodies are becoming more accepted for diagnosis and classification, including anti RNA polymerase III. With the availability of new laboratory techniques and the diffusion of large cohorts of pooled patients, new clinical associations have been described.

Anti SSA/Ro52 has been linked with interstitial lung disease. Autoantibody-negative SSc is rare (less than 2%) and associated with favorable outcomes.

Organ Involvement

Skin involvement is a frequent feature of SSc patients. SSc skin involvement has classically been divided into two subsets, involvement distally or proximally to the metacarpophalangeal joints.

"Modified Rodnan Skin Score (MRSS), remains the best method for the objective assessment of skin involvement both in clinical practice and in research settings that combines feasibility, an acceptable reliability, responsiveness to change and correlation with physician global correlates of health status,” the authors wrote.

Musculoskeletal Involvement

Synovitis and tendon friction rubs are associated with poor outcomes. Musculoskeletal manifestations are a major cause of morbidity and disability. Hand and face disability contribute significantly to global disability. A scoring system for hand callosities has been proposed. Low bone mineral density, which is common, could be caused by major organ involvement or by treatment.

Vascular Involvement

Microvascular changes are typically observed in the nail fold bed by capillary microscopy and is used for early diagnosis and prognosis. Similarly, digital ulcers are an early manifestation of vasculopathy and are a considerable burden on quality of life and function. Risk and predictive factors for digital ulcers have been identified, but digital ulcers are hard to treat. It is unclear whether they are caused by dysfunction in the digital arteries or microvasculature.

Pulmonary Involvement

Lung complications are a major cause of death in patients with systemic sclerosis. Interstitial lung disease and pulmonary artery hypertension are on a spectrum, which includes both diseases superimposed on each other. Interstitial lung disease is more prevalent and worse in African Americans, and the cause may be genetic rather than access to care or socioeconomic status. Prompt diagnosis and treatment could improve outcomes.

High resolution CT is the gold standard, and newer low-radiation protocols with fewer slices have been developed. Non-invasive methods, such as ultrasound, are emerging. Lung diffusion capacity for nitric oxide might be more sensitive than lung diffusion capacity for carbon monoxide.

In a large cohort of SSc subjects followed for 15 years, two-thirds of subjects had overt lung disease within five years, and it was associated with worse survival. The PHAROS registry is a prospective observational longitudinal cohort study to determine time to pulmonary hypertension and pulmonary artery hypertension for patients with different risk factors. Exercise-induced hypoxia is strongly associated with pulmonary hypertension.

Heart Involvement

Primary myocardial involvement results from the underlying vascular lesions and fibrosis that impairs microcirculation and myocardial function, and carries an ominous prognosis. Standard echocardiography is not sensitive to its detection, but new methods, such as tissue Doppler echocardiography or magnetic resonance disclose a high rate of heart involvement.

Gastro-Intestinal Involvement

Muscular fibrosis, present in as many as 43%, is associated with lower left ventricular ejection fraction and affects mainly basal left ventricular walls. SSc patients are at higher risk of cardiac arrhythmias, which is also associated with poor outcomes. Management is difficult, because SSc drugs can affect QTc prolongation, and because the clinical features of SSc limit the tolerability of anti-arrhythmic drugs.
Gastrointestinal involvement is the second most common manifestation after skin involvement. Esophageal and ano-rectal involvement are the earliest involvement. There is little published evidence to guide clinicians.

Small intestinal bacterial overgrowth is common and is treated with cycles of antibiotics, although recurrence is common, in part because proton pump inhibitors are a known risk factor.

Cancer

CT imaging of the chest is often used to monitor SSc, but the radiation is so high that it carries a risk of radiation-induced cancer. A group in northern Italy found a significant increase in breast cancer for SSc patients, even when matched for X-ray exposure.

Therapy

Immunosuppressive drugs are recommended in diffuse cutaneous SSc as early as possible to induce remission or at least low disease activity before damage occurs. Most interstitial lung disease patients present with stable or slowly progressive lung disease. Some have a rapidly progressive loss of lung function, usually within the first years, and only they should be treated with immunosuppressive drugs.

High risk of lung function decline is predicted by baseline lung fibrosis greater than 20%, forced vital capacity less than 70%. First-line cyclophosphamide can stabilize and even improve lung function, but its effects on lung function vanish after 6-12 months, so patients are switched to azathioprine or mycophenolate mofetil. When first-line cyclophosphamide fails, rituximab has been promising in small studies.

Other drugs are targeted at known signaling abnormalities of SSc. For example, platelet-derived growth factor and transforming growth factor-B (TGF-B) are key signaling molecules in excessive fibrosis, produced by fibroblasts as a response to tyrosine kinase. So tyrosine kinase inhibitors could be useful. Indeed, low-dose imatinib, a tyrosine kinase inhibitor, stabilized lung function.

Fresolimumab, a monoclonal antibody to transforming growth factor-B, improved skin disease. SSc fibroblasts produce high levels of interleukin-6, and a phase III trial of tocilizumab, a monoclonal antibody against interleukin-6, is underway.

Macitentan, an endothelin receptor antagonist, has improved the survival of patients with pulmonary arterial hypertension. Drugs with vascular effects already used for pulmonary arterial hypertension are being tried against digital ulcers; ambrisentan was promising in a pilot study. A randomized, placebo-controlled trial of sildenafil, the SEDUCE study, found that digital ulcers were more likely to heal in the sildenafil group.

Combination therapy with bosentan and sildenafil might be more effective. Hematopoietic stem cell transplantation has caused some improvements, although the high surgical mortality mandates caution. A randomized, controlled trial is evaluating the safety and effectiveness of intravenous immunoglobulins.


Source URL: http://www.rheumatologynetwork.com/systemic-sclerosis/annual-review-systemic-sclerosis-research

Links: