Update in Systemic Sclerosis

Lauren Kim MD
NW Rheumatology Associates
Review

- Systemic sclerosis affects approximately 75,000 to 100,000 people in the U.S. and has the highest mortality rate of any autoimmune rheumatic disease.
- More than 75% of patients are women, primarily ages 30-50 although there are outliers who are much younger and much older.
- There is no FDA approved therapy for this rare disease.
Review

Morphea: also known as localized scleroderma or circumscribed scleroderma
- Only affects skin
- Does not become systemic or go on to affect internal organs
- Can cause disfigurement

Systemic Sclerosis
- Can affect internal organs
- 2 types: Limited (also known as CREST) vs Diffuse
Review

Limited Scleroderma (also known as CREST)
- Usually ANA and/or anti-centromere +
- Affects skin up to forearm
- More likely to develop pulmonary hypertension which usually occurs at least 5 years after disease diagnosis

Diffuse Scleroderma
- Usually Scl-70 antibody (also known as topoisomerase ab) or RNA polymerase III antibody
- Diffuse skin disease
- More likely to have inflammatory lung disease
- More likely to have renal crisis
Both groups can have:

- Skin tightness of face
- Telangiectasias (red dots)
- Raynaud’s
- Calcinosis
- Heartburn
- Swallowing trouble
- Digestive problems
- Dry skin
Review

- Some patients can have overlap of rheumatoid arthritis
- Some patients can have overlap of muscle inflammation disease (myositis)
- Many patients also have dry eyes and dry mouth
Advances

- As many of you know, I’ve been talking about potential advances for a long time.
- Not much has panned out.
- For the first time, there is new hope in scleroderma.
- 3 major advances in scleroderma research were seen this past year.
Advances

faSSinate study:

- Data from phase II open label study of tocilizumab (brand name for RA Actemra) in patients with diffuse SSc
- Tocilizumab works in RA by getting rid of an inflammation chemical called IL-6 (interleukin 6)
- The study enrolled patients with modified Rodnan skin score of 15-40 (high) with less than 5 years of disease and elevated ESR or CRP levels (inflammation chemicals)
Modified Rodnan Skin Score
Advances

- Treated 87 SSc patients with weekly SQ injection of tocilizumab vs placebo for 48 weeks.
- From week 49 to 96, patients received open-label drug.
- The primary end point of significant change in mRSS was not achieved at 24 weeks but between 24 and 48 weeks, there was continued improvement in skin thickening.
- There was significantly less deterioration in their breathing test parameter called Forced Vital Capacity (FVC) measurement.
- The overall adverse event profile between both groups was comparable.
Advances

- These findings led to the FDA to grant “breakthrough” designation for TCZ in scleroderma.
- Breakthrough therapy designation from the FDA helps to expedite the development and review of drugs that are intended for the treatment of serious diseases and to provide access to patients as soon as possible.
- Genentech initiated a multicenter, randomized, double-blind, placebo-controlled Phase III trial.
Advances

● Report of a novel drug called fresolimumab

● This is an anti-TGF (transforming growth factor)-beta monoclonal antibody

● It is a secreted protein that performs many cellular functions including control of cell growth, proliferation, differentiation and apoptosis (programmed cell death)

● It is also an important player in the control of the immune system
Advances

- Fresolimumab blocks TGF-beta action in producing fibrosis

- 15 patients in the early stages of scleroderma were given this drug by IV

- The skin of each of the patients were biopsied before the drug was given then several times after the drug was administered

- Because mRSS takes a long time to change, they measured biomarkers on the skin biopsies instead
Advances

- Nearly all patients had significant and rapid decreases in the biomarker levels of thrombospondin-1 (THBS1) and cartilage oligomeric protein (COMP).
- MRSS decrease by a median of 8 points at week 11.
- This is the first report demonstrating the potential role of an anti-TGF-beta inhibition in scleroderma.
- Knowing which biomarkers correlate with skin change will help development of all kinds of new drugs for scleroderma.
Advances

- Comparison of mycophenolate mofotil versus cyclophosphamide in scleroderma related interstitial lung disease

- Scleroderma related interstitial lung disease is one of the most serious complication of the disease and leading cause of mortality early in disease

- Last study done by this same group (Scleroderma Lung Study Research Group which includes Dr. Dan Furst) compared cyclophosphamide versus placebo in this disease
Advances

- Although cyclophosphamide did help ILD to a degree, there were significant side effects which typically limits its use to 1 year.

- Cyclophosphamide can lead to significant infections, bleeding of the bladder and in some cases bladder cancer later in life.

- Looking for drugs that are similarly effective with less severe side effects.

- Mycophenolate has been used in scleroderma for many years for skin disease and lung disease but without hard clinical trial data.
Advances

● This is the first published study looking at the benefits of mycophenolate (MMF) for scleroderma.

● It compared MMF at 3 grams/day for 2 yrs to oral cyclophosphamide 2 mg/kg/day for 1 year followed by placebo for another year.

● These patients had FVC% between 40-60% predicted (moderate disease).

● One had to have disease for less than or equal to 7 years, had to have abnormalities on the CT scan of the lung (ground glass indicating active inflammation).
Advances

- There were 73 pts enrolled in the cyclophosphamide group and 69 patients in the MMF group.
- Twice as many patients in the cyclophosphamide group dropped out of the study.
- 2/3 of patients had improvement in skin score.
- There were 11 deaths in the cyclophosphamide group compared to 5 in the MMF group due to advancing disease.
- Overall MMF was better tolerated and at least equally efficacious.
Advances

● An abstract at the recent ACR meeting showed decrease in frequency of need for endoscopic treatments for GAVE in patients with scleroderma in patients on MMF

● There are ongoing new drug develops for pulmonary hypertension: Brand new drug approved is called Selexipag (Uptravi) – an oral selective prostacyclin IP receptor agonist.
Advances

- Other classes of PAH drugs include phosphodiesterase-5 (PDE5) inhibitors such as sildenafil (Revatio) and tadalafil (Adcirca), endothelin receptor antagonist such as ambrisentan (Letaris), bosentan (Tracleer), macitentan (Opsumit), soluble guanylate cyclase stimulator named riociguat (Adempas), prostacyclin agonist such as epoprostenol (IV), iloprost (Ventavis-inhaled), Remodulin (SC or IV), Tyvaso (inhaled), treprostinil (Orenitram-oral)
Conclusion

- Systemic sclerosis is a rare and potentially life-threatening condition.
- No FDA approved drug currently exist for the disease so we treat the individual manifestations of the disease such as heartburn and raynaud’s.
- There is exciting ongoing research in the field.
- I hope to see drugs to treat the actual disease within the next decade.