RhAPP

RHEUMATOLOGY ADVANCED PRACTICE PROVIDERS

Inaugural National Conference

December 3 – 5, 2020

VIRTUAL CONFERENCE

RhAPP
RHEUMATOLOGY ADVANCED PRACTICE PROVIDERS

The Steffens Scleroderma Center
Breaking the Chains

The Center for
RHEUMATOLOGY LLP
Diagnosis, Care and Research

Scleroderma

Jessica Farrell, PharmD.

Clinical Pharmacist- The Center for Rheumatology
Associate Professor, Department of Pharmacy Practice
Albany College of Pharmacy & Health Sciences

ALBANY COLLEGE OF PHARMACY AND HEALTH SCIENCES

Amanda Mixon, PA-C

Colorado Center for Arthritis and Osteoporosis
Longmont, CO

Disclosure

All faculty and staff involved in the planning or presentation of continuing education activities provided by the Annenberg Center for Health Sciences at Eisenhower (ACHS) are required to disclose to the audience any real or apparent commercial financial affiliations related to the content of the presentation or enduring material. Full disclosure of all commercial relationships must be made in writing to the audience prior to the activity. All staff at the Annenberg Center for Health Sciences at Eisenhower and Rheumatology Advanced Practice Providers (RhAPP) have no relationships to disclose.

Faculty Disclosures

Jessica Farrell, PharmD:

- There are no relevant conflicts of interest related to the subject matter in this presentation.
- Consultant, Independent Contractor, Advisory Boards: Cumberland Pharma, Gilead, Boehringer Ingelheim, Pfizer, and AbbVie.
- Program Coordinator for a PGY-2 Ambulatory Care Residency program which receives partial salary support funding from Janssen Pharmaceuticals.

Amanda Mixon, PA:

- There are no relevant conflicts of interest related to the subject matter in this presentation.

Learning Objectives

- Review pathophysiology of scleroderma and common clinical presentation
- Review management of common disease states associated with scleroderma

Scleroderma (Systemic Sclerosis)

- A multisystem disease characterized by widespread vascular dysfunction and progressive fibrosis of the skin and internal organs
  - i.e. thickened hardened skin
- Two types
  - Limited Cutaneous (CREST Syndrome or lcSSc) ~60%
  - Diffuse Cutaneous (dcSSc) ~30%

Limited Cutaneous (CREST Syndrome)

- Skin involvement limited to hands, distal forearms, and to a lesser extent face and neck
- Vasculopathic phenotype
- Crest Syndrome
  - Calcinosis Cutis
  - Raynaud Phenomenon
  - Esophageal dysmotility
  - Sclerodactyly
  - Telangiectasia
- Anti-Centromere Ab (70-80%)
- Pulmonary Hypertension (late complication ~10%)

Diffuse Cutaneous (dcSSc)

- Skin involvement on chest, abdomen, upper arms and shoulders
  - Thickening process will continue for 1-3 years after diagnosis then slow down
- Onset of Raynaud's within 1 year of skin involvement
- Fibrotic phenotype
- Tendon friction rubs
- More likely to develop internal organ damage often early on
  - ILD, Renal failure, diffuse GI disease, and myocardial involvement
- SCL-70 Ab
- Higher mortality

Limited and Diffuse SSc— Skin Involvement

2013 ACR/EULAR Classification criteria for SSc

Item	Sub-item(s)	Weight/score
Skin thickening of fingers of both hands extending proximal to mcps		9
Skin thickening of fingers	Puffy fingers	2
	Sclerodactyly of fingers	4
Finger-tip lesions	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia		2
Abnormal nailfolds		2
PAH +/- ILD		2
Raynaud's phenomenon		2
SSc related autoantibodies	ACA	3
	Anti-topo 1	
	Anti-RNAP 3	

Auto-Antibodies Can Predict Organ Involvement

Scl-70 antibody

Th/To Progressive ILD

U3 RNP

U11/12 RNP

Centromere Ab Pulmonary Arterial Hypertension

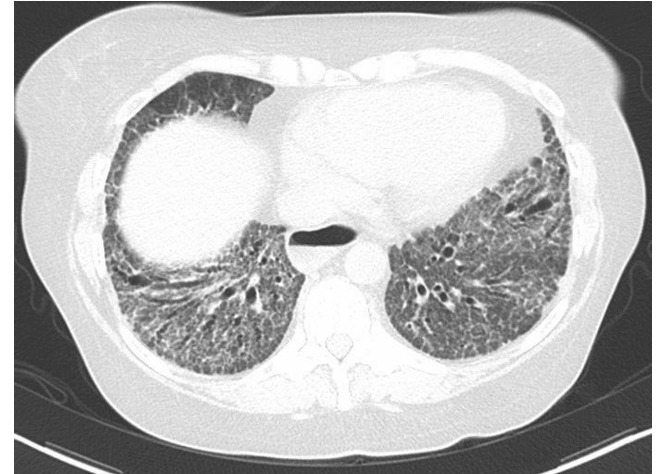
RNA- Polymerase 3 Ab Scleroderma Renal Crisis

When SSc Is Suspected, You Should Order:

- Labs
  - Pos ANA
    - Centromere ab or SCL 70 Ab
    - Scleroderma panel can also be drawn
- Chest X-Ray
- PFT with DLCO
- HRCT scan of the lungs
- Esophagram
- Echocardiogram complete

Interstitial Lung Disease

- Most common SSc Lung disease and leading cause of death in SSc
- ILD more common in Diffuse Scleroderma (50% of patients), often early on. 25% of patients with limited
  - PFTs with FVC <70% and reduced DLCO <50%
  - CT evidence of ground glass, honeycombing, or bronchiectasis



Solomon et al. *Eur RespReviews*. 2013.
Picture courtesy of Dr. Aryeh Fischer MD.

Pulmonary Hypertension

- 10-15% of patients (later complication)
  - Anti-Centromere Ab associated with higher likelihood, usually 10-15 years after Raynaud's
  - Yearly echocardiogram, may need R heart cath
  - May start with mild dyspnea on exertion

Scleroderma Renal Crisis

- IMPORTANT! This is a medical emergency
- Occurs in 5-20% of diffuse scleroderma, most always within 5 years of the diagnosis
- 3 Major features
  - Abrupt onset of moderate to severe hypertension
  - Acute Kidney Injury
  - Urinalysis that is normal or reveals only mild proteinuria with few cells or casts
- RNA Polymerase Ab, extensive skin involvement, and glucocorticoid use all risk factors
- If left untreated, patients can go into end stage renal disease within 1-2 months and death usually within 1 year

Scleroderma Renal Crisis

- Prevention!
  - Always check blood pressures at every visit
  - Don’t give steroids!
- Prompt blood pressure control
  - ACE Inhibitors – Captopril preferred
    - Short onset of action (60-90 minutes)
    - Starting dose of 6.25mg-12.5mg with dose escalation in 12-25mg increments every 4-8 hours until goal blood pressure is reached. Max dose 300-450mg
    - Goal to get back to baseline BP within 72 hours to prevent permanent damage

Other Disease Manifestations

- Arthritis
  - Consider Methotrexate, Leflunomide
  - Biologics: Abatacept or Tocilizumab
- Myositis (often more severe and refractory to treatment)
  - Associated with PM-Scl and fibrillarin antibodies
  - Methotrexate, Mycophenolate, and Rituximab all used
- Sjogren’s Syndrome
  - Preservative free eye drops
  - Proper ophthalmic and dental care
  - Pilocarpine or Cevimeline
  - ? hydroxychloroquine

Malignancy

- Risk of cancer increased in both diffuse and limited
  - Two-fold increased risk
    - Lung, Breast, Hematologic, and Melanoma most common
    - Lung cancer associated with ILD
    - Breast cancer and melanoma occurring close to SSc disease onset in association with RNAP III antibodies

General Principles for Treatment

No single drug therapy has been found to treat all aspects of scleroderma

Treatment is individualized & organ-specific

Targeted at treating inflammation, autoimmunity, vascular disease, and tissue fibrosis

Routine screening and early treatment for internal organ manifestations to improve disease outcomes

Pharmacologic Treatments

- Raynaud's
  - BP medications
  - Vasodilating drugs
- GI Medications:
  - Antacids
  - Motility medications
  - Antibacterial
- Joint/Tendon Pain:
  - NSAIDS: Ibuprofen, naproxen, diclofenac, celecoxib
  - Analgesics: acetaminopen, tramadol, opioids, antidepressants
  - Corticosteroids
- Immunosuppressants:
  - Methotrexate
  - Mycophenolate mofetil
  - Cyclophosphamide
- Pulmonary Hypertension
  - Vasodilating drugs
  - Anti-fibrotics
- Renal Crisis
  - ACE-Inhibitors

Kowal-Bielecka O et al. *Ann Rheum Dis*. 2017; 76:1327; Frech TM et al. *Clin Exp Rheumatol.* 2013; 31:166;
Herrick AL et al. *Ann Rheum Dis*. 2017; 76:1207; Kowal-Bielecka O et al. *Ann Rheum Dis*. 2009; 68:620.

Labeled Indication vs Off-Label

FDA-approved indication

Use often supported by multiple, large, randomized clinical trials

Generally more common diseases

Off-label use

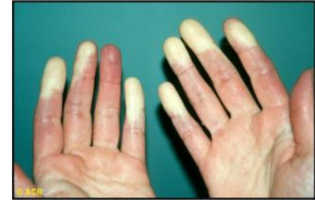
Use of medication outside approved indication

Evidence available to support the use

Extent of evidence varies, less than what is required for FDA approval

Wittich CM, et al. *Mayo Clin Proc*. 2012;87(10):982-990.

Raynaud’s Phenomenon



Drug Class	Drug Names	General Side Effects
Calcium Channel Blocker (CCB)	nifedipine, amlodopine	Hypotension, flushing, dizziness, peripheral edema
Angiotensin Receptor Blocker (ARB)	Losartan, valsartan	Dizziness, diarrhea, hypotension, muscle cramps, and headache
Alpha Blockers	Prazosin	Hypotension, dizziness, drowsiness
Nitrates	Topical Nitroglycerin 2%	Rash, headache, facial flushing, dry mouth, hypotension, tachycardia
Phosphodiesterase-5 Inhibitors (PDE-5i)	Sildenafil Tadalafil	Blurred vision, flushing, headache, hypotension, visual impairment, tachycardia

Raynaud's & Digital Ulcers

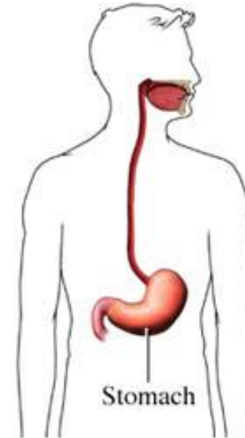
Drug Class	Drug Names	General Side Effects
Phosphodiesterase-5 Inhibitors	Sildenafil Tadalafil	Blurred vision, flushing, headache, hypotension, visual impairment, tachycardia
Prostacyclin/ prostacyclin analog	Epoprostenol Treprostinil Iloprost	Hypotension, dizziness, muscle cramps, peripheral edema, headache *Administration concerns
Endothelial Receptor Blockers	Bosentan Ambrisentan	Liver injury, headache, flushing, leg swelling, fatigue, hypotension, itching, and weight gain *REMS program

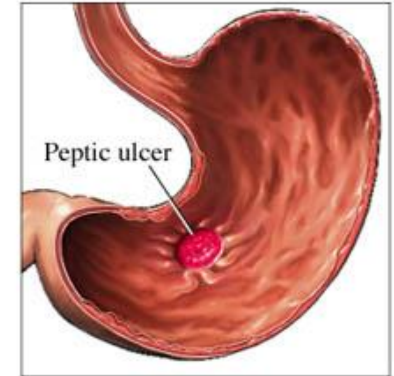
Raynaud's: Agents to Avoid

- NICOTINE!
- Caffeine
- Amphetamine
- Beta-blockers (propranolol, metoprolol, atenolol)
- Pseudoephedrine (includes combo products!)
- Migraine meds
- Clonidine

Pain Management: Concerns in Scleroderma

- NSAIDS (ibuprofen, naproxen, etc)
  - Esophageal concerns
  - Gastritis (damage to GI lining)
- Steroids
  - Risk for renal crisis
    - Caution/Avoid if RNA- Polymerase 3 antibody
- Opioid Pain Meds
  - Decreased motility in GI tract
    - Constipation in general population → may be exaggerated in scleroderma patients
  - Risk of respiratory depression
  - May require a multimodal approach

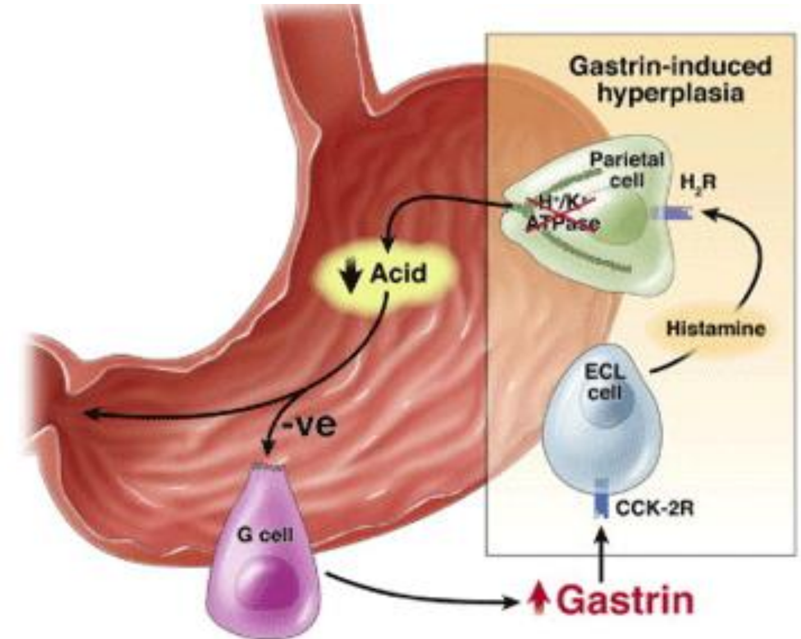




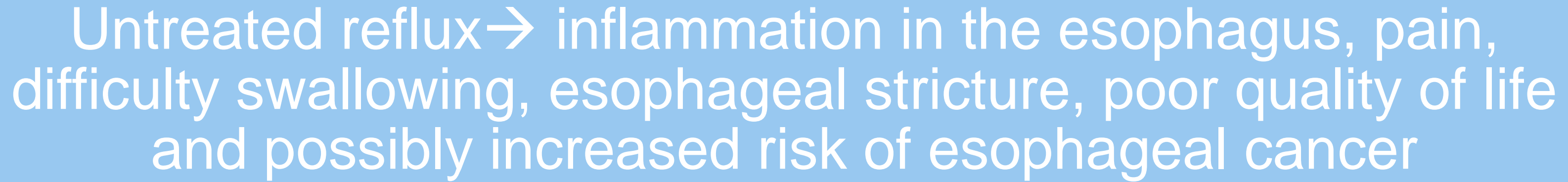
Steen VD, Medsger TA Jr. *Arthritis Rheum*. 1998; 41:1613.

GI Treatment: Antacids

- 1st Line: Proton Pump Inhibitors (PPIs)
  - Omeprazole
  - Lansoprazole
  - Esomeprazole
  - Rabeprazole
  - Pantoprazole
  - Dexlansoprazole
- 2nd Line: H-2 Blockers (H2RAs)
  - Ranitidine
  - Famotidine
- Side effects:
  - GI symptoms, decreased absorption of vitamins (calcium, magnesium, etc.)



PPI's Risk vs Benefit



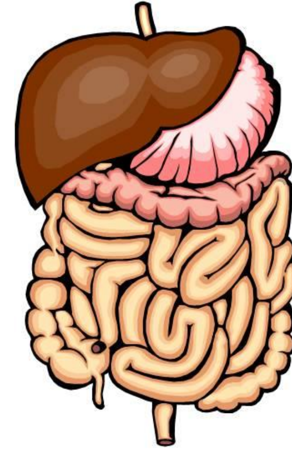
A trial of an H2RA is reasonable

Options include using once daily PPI plus H2RA at bedtime or H2RA twice daily

Freedberg DE et al. *Gastroenterology*. 2017; 152:706.

GI Treatments

- Small Bowel Bacterial Overgrowth
  - Cyclic antibiotic therapy
- Promotility Agents
  - Metoclopramide
    - Long term use – movement disorders
  - Domperidone (not available in US)
    - Risk of heart problems
    - Potential drug interactions
  - Risk vs Benefits



TEAM APPROACH:
MD & Pharmacist!

GI Symptoms: Agents to Avoid

⇩ GI Movement

- Narcotic pain meds
- Tricyclic antidepressants
  - Amitriptyline/Nortriptyline
- Iron supplements
- Anti-Parkinson’s meds
- Verapamil
- Anti-histamines
  - Diphenhydramine

⇧ GI Movement

- Laxatives
- Erythromycin
- Orlistat
- Muscle relaxants
- Risperidone
- Colchicine
- Magnesium
- Others

RhAPP
RHEUMATOLOGY ADVANCED
PRACTICE PROVIDERS

Immunosuppressants and Biologics

Conventional DMARDs/ Immunosuppressants in SSc

Drug	Use in SSc	ADRs	Monitoring/Counseling	Medication Errors
Methotrexate	Diffuse cutaneous Inflammatory arthritis Inflammatory myopathy	N/D, hepatotox, stomatitis, alopecia, SOB, myelosuppression (MYL)	CBC, Scr, LFTs q 4-8 weeks, signs of infection; pregnancy Concomitant use of folic acid, avoid alcohol, use of contraception	WEEKLY dosing, dose adjustments, drug interactions, lab monitoring
Mycophenolate mofetil Mycophenolic acid	Interstitial lung disease Diffuse cutaneous	GI upset (DIARRHEA), increased risk of infection, headache, elevated liver enzymes, peripheral edema, leukopenia, thrombocytopenia	CBC, serum electrolytes, liver enzymes, kidney function; drug interactions; **REMS (pregnancy)**	**REMS**, do not crush, PPI interactions
Azathioprine	Diffuse cutaneous Inflammatory myopathy	GI upset, myalgia, leukopenia, thrombocytopenia, risk of infection, elevated hepatic enzymes, alkaline phosphatase and bilirubin	Signs of bleeding, sx of jaundice, change in color of stool; TPMT deficiency, drug interactions	Community high-alert med, error prone abbreviations (AZT for zidovdine), dose reductions
Cyclophosphamide	Interstitial lung disease Diffuse cutaneous Inflammatory myopathy	Hair loss, GI upset, decreased appetite, stomatitis, amenorrhea, myalgia, nail discoloration, interstitial cystitis, infertility, oligospermia/azoospermia, Stevens-Johnson syndrome, increased risk of bladder cancer	CBC, urinalysis (monthly if on IV therapy)	Look-alike/sound alike-cyclosporine, community high-alert med; do not crush list, error prone abbreviations

https://www.ismp.org

Biologics Used in SSc

Drug	Use in SSc	ADRs	Monitoring
Abatacept *T-cell Costimulation Modulator*	Inflammatory arthritis	Injec.site rxn, HA, dizziness, cough, nasopharyngitis	Screen for TB, Signs of infection, respiratory w/ COPD pts. ****infection risk clinically lower than other biologics**
Rituximab *B-cell Modulator*	Interstitial lung disease Diffuse cutaneous Inflammatory myopathy	Infusion rxn (rash, N, SOB, urticaria, HA, fever, chills) Methylpred 100mg 30 min prior & diphenhydramine	Signs of infection, post infusion rxn, **Progressive multifocal leukoencephalopathy (PML)**- neurology s/sx
Tocilizumab *IL-6 inhibitor*	Interstitial lung disease Diffuse cutaneous	Infus. rxn, ↑ risk of infection, **anemias, ↑ lipids/ liver enzymes, GI sx**	↑ risk of infection ANC, LFTs, platelets, lipids, GI symptoms; **drug intx**

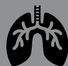
N/V/D=nausea, vomiting, diarrhea; HA=headache; TB=tuberculosis; ANC=absolute neutrophil count

Pulmonary Manifestations

- Interstitial fibrosis
  - Earlier manifestation
- Pulmonary Arterial Hypertension (PAH)
  - Late manifestation

- Therapies used:
  - Immunosuppressants
    - MMF, CYC, rituximab
  - Phosphodiesterase-5 Inhibitors:
    - Sildenafil
    - Tadalafil
  - Prostacyclin Agonists:
    - Epoprostenol
    - Treprostinil
    - Iloprost
  - Endothelial Receptor Blockers:
    - Bosentan
    - Ambrisentan
    - Macitentan
  - Soluble Guanylate Cyclase (sGC) Stimulator
    - Riociquat

Nintedanib for Systemic Sclerosis-Associated Interstitial Lung Disease



Slower rate of decline in lung function over 1 year versus placebo

Sensitivity analyses failed to show a significant difference, though there was still a trend towards better outcomes with nintedanib

Does NOT seem to affect skin involvement or other disease manifestations

Role in therapy is uncertain; may be best to reserve for patients failing Cellcept until more data are available

- 48.8% of patients were on mycophenolate mofetil at baseline

Most common adverse effects were diarrhea (occurring in 75.7% of patients in this clinical trial)

Other adverse events included nausea, vomiting, fatigue, and weight loss

No major difference in serious ADEs was observed

Distler O et al. *N Engl J Med*. 2019;380(26):2518-28.

Drug Interactions

- Importance of a good medication history
  - Supplements, OTC's, infusions/injections
- Oftentimes dose-dependent
  - Ex: methotrexate and NSAIDs, antidepressants combinations
- May be able to manipulate schedule to avoid interaction
  - Spacing medications apart (ex: levothyroxine, omeprazole, mycophenolate mofetil)

RhAPP

RHEUMATOLOGY ADVANCED
PRACTICE PROVIDERS

Thank you.

Key References

- Denton CP, Khanna D. *Lancet*. 2017; 390: 1685–99.
- Kowal-Bielecka O, Fransen J, Avouac J, et al. Update of EULAR recommendations for the treatment of systemic sclerosis. *Ann Rheum Dis*. 2017; 76:1327.
- Frech TM, Shanmugam VK, Shah AA, et al. Treatment of early diffuse systemic sclerosis skin disease. *Clin Exp Rheumatol*. 2013; 31:166.
- Herrick AL, Pan X, Peytrignet S, et al. Treatment outcome in early diffuse cutaneous systemic sclerosis: the European Scleroderma Observational Study (ESOS). *Ann Rheum Dis*. 2017; 76:1207.
- Kowal-Bielecka O, Landewé R, Avouac J, et al. EULAR recommendations for the treatment of systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group (EUSTAR). *Ann Rheum Dis*. 2009; 68:620.
- Steen VD, Medsger TA Jr. Case-control study of corticosteroids and other drugs that either precipitate or protect from the development of scleroderma renal crisis. *Arthritis Rheum*. 1998; 41:1613.

Key References Cont…

- Solomon et al. *Eur RespReviews*. 2013.
- Morrisroe K, et al. *Arthritis Care Res*. 2019: 10.1002/acr.24076
- Fischer A, et al. *Arthritis Care Res.* 2012;64;303-310
- https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-systemic-sclerosis-scleroderma-in-adults/abstract/1