Raynaud’s Phenomenon and Digital Ischemia

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• All of the medications in this presentation are discussed for use for non FDA-approved indications
Goals

• Review the factors that increase risk for CTD among those with RP
• Briefly discuss the relevant pathophysiology of Raynaud phenomenon and digital ischemia in scleroderma
• Review unique situations in scleroderma
• Discuss established therapies and those currently in trial
• Review possible treatment algorithms

Raynaud’s Phenomenon
What is and is not Raynaud’s:

- Palmar
- Symmetric
- Sharp Demarcation

NOT:

- Mottling (non-specific)
- Fingernails only
- Unilateral

Blood Vessel Structure
Peripheral Vascular Disease

Secondary Raynaud’s Phenomenon/Mimics-Differential Diagnosis

- Immune: Autoimmune Disease (Scleroderma, Lupus, Myositis, UCTD)
- Trauma: Hand-Arm Vibration Syndrome
- Mechanical: Thoracic Outlet Syndrome
- Proteins: Cryoglobulins; Cryofibrinogens
- Neurogenic: Carpal Tunnel Syndrome
- Hormones: Estrogens
- Toxins/Drugs/Vasoconstrictors: Smoking (TAO), sympathomimetics, chemotherapy, polyvinyl chloride, cocaine (levamisole)
- Vascular disease: Diabetes, Vasculitis, etc.
Physical Exam Findings

Predictors of Development of CTD/Scleroderma

- Abnormal nailfold capillaries
  - Nailfold dilatation/Dropout (avascular areas)
  - HR 14-18 for development of SSc
- Autoantibodies
  - 30% risk of CTD if just ANA positive
  - HR 10-23 for SSc with just ANA positivity
- Both abnormal NFC and SSc antibody
  - HR 60
- Negative ANA, normal nailfold capillaries have high NPV (>95%)

Classification of Systemic Sclerosis

Table 1. The American College of Rheumatology/European League Against Rheumatism criteria for the classification of systemic sclerosis (SSc)*

<table>
<thead>
<tr>
<th>Item</th>
<th>Sub-score(s)</th>
<th>Weight/score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin thickening of fingers (not count the higher score)</td>
<td>–</td>
<td>2</td>
</tr>
<tr>
<td>Skin thickening of fingers (not count the higher score)</td>
<td>–</td>
<td>4</td>
</tr>
<tr>
<td>Fingertip lesions (not count the higher score)</td>
<td>–</td>
<td>2</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>–</td>
<td>2</td>
</tr>
<tr>
<td>Abnormal nailfold capillaries</td>
<td>–</td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary arterial hypertension and/or interstitial lung disease (maximum score 2)</td>
<td>–</td>
<td>2</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>–</td>
<td>3</td>
</tr>
<tr>
<td>Scleroderma autoantibodies (anti-Scl-70, anti-topoisomerase I, anti-RNA polymerase II)</td>
<td>Anti-Scl-70</td>
<td>3</td>
</tr>
</tbody>
</table>

*Nailfold Capillary changes

Method:
- Drop of Immersion Oil on Nailfold
- Ophthalmoscope at +40 diopters (10x magnification)
- OR
- Dermatoscope
Complications

Digital Ischemic Ulcers
### Risk Factors of Digital Ulcerations

- **Digital loss (10%)**
  - Anti-centromere antibody
  - Multiple prior digital ulcerations
  - Large vessel involvement (ulnar artery)
  - Older age, long disease duration, PAD, HLD

- **Ulcers (50%)**
  - Centromere and topo (not Pol III)
  - Smoking?

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### Acute digital ischemia

- **Ischemic?**
  - Severe pain
  - Location
  - Surrounding hyperemia

- **Therefore:**
  - At risk for further tissue loss and continued pain
  - Pain triggers sympathetic response
  - At risk for further ischemia

- 58% of scleroderma patients with digital ulcerations
- 11% with severe disease (gangrene, amputation)

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Non (or less) Ischemic Ulcers

Management
Behavior Modification

- Avoid cold
- Stress reduction
- Layers
- Ambient temperature
- Hand warmers
- Biofeedback

Local Care

Cleansing
- Warm soapy water soaks a few times per day

Protection
- Covering with bandage, wrap if going to be using hands

Infection
- Antibacterial ointment (mupirocin)

Pain
- Topical Anesthetics (lidocaine)
**Targets for Therapy**

![Diagram showing targets for therapy](image)

**Calcium Channel Blockers**

*All calcium channel blockers vs. placebo*

- (6 trials): Reduction of frequency of attacks in a 2-week period of **-8.31** (95% CI: -15.71, -0.91)
- (3 trials): Reduction in severity of ischemic attacks of **-0.69** (95% CI: -1.21, -0.17)

*Thompson et al., 2001*
Symptoms of the 16 study patients with secondary Raynaud’s phenomenon while taking sildenafil and placebo

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Sildenafil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Raynaud Attacks during 4 weeks</td>
<td>3.76</td>
<td>2.43</td>
</tr>
<tr>
<td>p-value</td>
<td>0.0064</td>
<td></td>
</tr>
<tr>
<td>Cumulative Duration of Raynaud Attacks during 4 Weeks</td>
<td>2.93</td>
<td>2.08</td>
</tr>
<tr>
<td>p-value</td>
<td>0.0038</td>
<td></td>
</tr>
<tr>
<td>Raynaud’s Condition Score (daily mean during 4 weeks)</td>
<td>53.4</td>
<td>40.6</td>
</tr>
<tr>
<td>p-value</td>
<td>0.0386</td>
<td></td>
</tr>
</tbody>
</table>

Oral Tadalafil

- Scleroderma patients off all treatment for Raynauds (N=39)
- 20 mg of tadalafil daily for 4 weeks compared with placebo
- Medication was found to be well tolerated

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Tadalafil</th>
<th>Placebo</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCS</td>
<td>3.76</td>
<td>2.43</td>
<td>2.53</td>
<td>NS</td>
</tr>
<tr>
<td>Raynauds Frequency</td>
<td>2.93</td>
<td>2.08</td>
<td>2.1</td>
<td>NS</td>
</tr>
<tr>
<td>Raynauds Duration</td>
<td>53.4</td>
<td>40.6</td>
<td>47</td>
<td>NS</td>
</tr>
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</table>

Tadalafil – ACR 2010

- Randomized controlled trial, tadalfil vs. placebo
- 53 scleroderma patients treated for 8 weeks
- Baseline treatments remained the same
- Improvements seen in duration and frequency of Raynaud and in RCS
- 14/18 had healing of digital ulcers compared with 5/13 in placebo arm
- Fewer new ulcers in tadalafil group than placebo (1 vs. 9)

Agarwal et al. Plenary session III, ACR national meeting October, 2010

Bosentan

- Dual endothelin receptor antagonist, FDA approved to treat pulmonary hypertension
- 2 Large, Phase III studies in patients with digital ulcers secondary to scleroderma (RAPIDS1, RAPIDS2, open label extension)
- 312 patients total
- Fixed dose titration 62.5 BID to 125 BID
- Primary outcome: # new digital ulcers; time to healing (RAPIDS2)
  - RAPIDS 1: 2.7 vs. 1.4 new ulcers at 16 weeks (p=0.178); 2 post hoc analyses (p=<0.01)
  - RAPIDS2: 2.7 vs. 1.9 new ulcers at 24 weeks (p=0.04)

Digital Ulcers prevention with mAcitentan in systemic scLerosis

- 285 patients, 75 centers, 30 countries
- 2 active doses vs. placebo (1:1:1); parallel
- Macitentan is a dual, tissue targeting ERA
- Inclusion:
  - Baseline ulcer + history of ulcers in past 6-12 months
- Outcomes:
  - # of new digital ulcers at 16 weeks
- Trial ended early due to lack of efficacy
- No adverse safety signals

Oral Treprostenil

- Long acting, chemically stable, prostacyclin analogue
- Phase I/IIb study
Oral Treprostenil

- 148 scleroderma patients at 27 centers
- Randomized 1:1 to oral treprostenil vs. placebo for 20 weeks
- At 20 weeks there was no change in net ulcer burden
- Other outcomes did improve including: physician and patient impression of improvement, Raynaud symptoms, hand function


Why the discrepancies?

- How to evaluate an ulcer?

- Is this an ulcer?
- Is it “active”?
- Is it healing?
Summary of Agents

- **Calcium Channel blockers**: Nifedipine, amlodipine, felodipine
- **Nitric oxide**: Nitrates (?topical)
- **Phosphodiesterase inhibitors**: Sildenafil, Tadalafil, Udenafil, Vardenafil
- **Selective Serotonin Reuptake inhibitors**: Fluoxetine
- **Angiotensin receptor inhibitor**: Lorsartan
- **Endothelin-1 inhibitor**: Bosentan, Ambrisentan, Macintan
- **Prostacyclins**: epoprostenol, treprostinil, iloprost
- **sGC stimulators**: Riociguat
- **Other**: Statins, ASA, pentoxyphyline, Botulium toxin A

Treatment Algorithm- RP

1. Symptomatic Raynaud
2. Behavior Modification/Cold and Stress Reduction
3. Initiate CCB therapy and titrate to effect/intolerance
4. Consider addition of losartan, fluoxetine, sildenafil if CCB alone ineffective
Management for Raynaud/Digital Ischemia: Evidence

<table>
<thead>
<tr>
<th>Agent Class</th>
<th>Type of Evidence</th>
<th>Positive outcomes</th>
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</thead>
<tbody>
<tr>
<td>Calcium channel blockers</td>
<td>RCT</td>
<td>Raynaud frequency and duration</td>
</tr>
<tr>
<td>Endothelin receptor antagonists</td>
<td>RCT</td>
<td>Reduction in new digital ulcerations</td>
</tr>
<tr>
<td>IV prostaglandins</td>
<td>RCT</td>
<td>Raynaud frequency, duration, severity; healing of ulcers</td>
</tr>
<tr>
<td>Phosphodiesterase inhibitors</td>
<td>RCT/conflicting</td>
<td>Raynaud frequency, duration, Raynaud condition score, ulcer healing</td>
</tr>
<tr>
<td>Surgical sympathectomy</td>
<td>Case reports/series</td>
<td>Ulcer healing</td>
</tr>
</tbody>
</table>

Galluccio F, Matsu-Cerinic, Autoimmunity Reviews. 10 (20110 241-3.
Shenoy PD et al. Rheumatology 2010; 49; 2420-8
Schiopu E et al. J Rheumatol 2009; 36:2264-8

Digital Ischemia/Ulcers

- **Acute Management**
  - Pain control (narcotics)
  - Aspirin
  - Epoprostenol
    - Peripheral IV
    - 0.5-2 ng/kg/min
    - 6 hours daily
    - 3-5 days
    - Inpatient/outpatient
  - Consider digital sympathectomy

- **Chronic Management**
  - Topical antibiotics
    - With lidocaine
  - Soaking
  - Pain control
  - Adjust chronic meds
    - Titrate CCB
    - Add second line agent
      - ERA
      - PDE5
  - Watch for additive side effects
Conclusions

• Raynaud is a common phenomenon
• History/exam can help distinguish primary vs. secondary and can identify those at risk for early scleroderma and Raynaud mimics
• Patients with CTD have more severe phenotype due to combination of vasospasm and intrinsic vessel disease
• Numerous potential targets for therapy