What’s new in Scleroderma?

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St Joseph’s Hospital
Medical Grand Rounds January 2014
Objectives

• To outline the multitude of systemic features of systemic sclerosis
• To discuss practical strategies to improve quality of life
• To highlight key advances in the investigation and management of systemic sclerosis
Scleroderma (Systemic Sclerosis) is ...

“sclero” (Greek meaning **hard**) + “derma” (Latin meaning **skin**)

= **scleroderma** (hard skin)

- Hippocrates
- 1945 association with systemic disease
### Terminology

<table>
<thead>
<tr>
<th>Localised</th>
<th>Systemic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphea</td>
<td>Limited skin disease to distal to elbows or knees (aka CREST)</td>
</tr>
<tr>
<td>Linear (eg en coup de Sabre – “Harry Potter sign”)</td>
<td>Diffuse proximal skin thickening</td>
</tr>
</tbody>
</table>

Images from ACR image bank
Terminology

- Localised
  - Morphea
  - Linear (en coup de Sabre)
  - Localised (distal to elbows or knees)
- Systemic
  - Diffuse
  - Sine Scleroderma (internal organs only)
Many aspects of scleroderma

- **Vascular system**
  - Raynauds
  - Healed pitting ulcers in fingertips
  - Cutaneous and mucosal telangiectasia

- **Gastrointestinal system**
  - GERD, GAVE
  - Dysmotility
  - Constipation /diarrhea

- **Respiratory system**
  - ILD
  - Pulmonary hypertension

- **Musculoskeletal system**
  - Arthritis/myositis
  - Flexion contractures
  - Carpal tunnel syndrome
  - Muscle weakness

- **Constitutional: Fatigue/weight loss**

- **Skin**
  - Sclerodactyly
  - Edema
  - Digital ulcers
  - Calcinosis
  - Hyper or hypo-pigmentation

- **Cardiovascular system**
  - Pulmonary hypertension
  - Arrhythmias

- **Genitourinary system**
  - Erectile dysfunction
  - Dyspareunia

- **Ears, nose, and throat**
  - Sicca syndrome
  - Poor dentition
  - Hoarseness due to acid reflux with vocal cord inflammation or fibrosis

- **Endocrine system**
  - Hypothyroidism

- **Renal system**
  - Hypertension
  - Renal crisis
  - Chronic renal insufficiency
## Limited vs Diffuse systemic sclerosis

<table>
<thead>
<tr>
<th></th>
<th>Limited (CREST)</th>
<th>Diffuse</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin Involvement</strong></td>
<td>Distal to elbows, knees, face</td>
<td>Distal &amp; proximal extremities, face &amp; trunk</td>
</tr>
<tr>
<td><strong>Raynaud’s Phenomena</strong></td>
<td>May precede skin changes by many years</td>
<td>May occur simultaneously or 1-2 years prior/after onset of skin disease</td>
</tr>
<tr>
<td><strong>Internal organ involvement</strong></td>
<td>GI, lung, heart</td>
<td>GI, lung, heart, kidney</td>
</tr>
<tr>
<td><strong>Nail fold capillaries</strong></td>
<td>Dilation without dropouts</td>
<td>Dilation with dropouts</td>
</tr>
<tr>
<td><strong>Antinuclear antibodies</strong></td>
<td>Anticentromere</td>
<td>Antitopoisomerase-1 (Scl70)</td>
</tr>
<tr>
<td><strong>Disease course &amp; prognosis</strong></td>
<td>Slowly progressive, better prognosis except with PAH</td>
<td>Aggressive course in majority, risk of early visceral involvement</td>
</tr>
</tbody>
</table>

## Specific Antibodies

<table>
<thead>
<tr>
<th>Autoantibody</th>
<th>Subtype (% subtype with antibody)</th>
<th>Clinical Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antinuclear antibody</td>
<td>Limited cutaneous &amp; diffuse cutaneous (95% nucleolar pattern is most specific)</td>
<td>Pulmonary arterial hypertension; Interstitial lung disease</td>
</tr>
<tr>
<td>Anticentromere antibody</td>
<td>Limited cutaneous (60 – 80%)</td>
<td>Pulmonary arterial hypertension</td>
</tr>
<tr>
<td></td>
<td>Diffuse cutaneous (2 - 5%)</td>
<td>Digital ulcerations or digital loss</td>
</tr>
<tr>
<td>Antitopoisomerase-1 antibody (anti-Scl-70)</td>
<td>Diffuse cutaneous (20 - 40%)</td>
<td>Rapidly progressive skin thickening; Scleroderma renal crisis; Pulmonary fibrosis</td>
</tr>
</tbody>
</table>

Nailfold capillaroscopy
ACR criteria 1980

Major criterion:

• Proximal diffuse sclerosis (skin tightness, thickening, non-pitting induration)

Minor criteria - 2 of 3:

• Sclerodactyly

• Digital pitting scars or loss of substance of the digital fingerpads (pulp loss)

• Bilateral basilar pulmonary fibrosis

1980 Criteria for the Classification of Systemic Sclerosis, American College of Rheumatology.
Outcome: Diffuse versus Limited

- Raynaud's, digital ischemia
- Esophageal dysmotility
- ILD
- Renal crisis

Adapted from www.Clevelandclinicmeded.com
Outcome – 75% 10 yr survival

• Causes of death
  – Pulmonary hypertension (major prognostic factor)
  – Pulmonary fibrosis
  – Scleroderma renal crisis

• 10 year survival rates:
  – Limited: 90%
  – Diffuse: 60%

(age and gender adjusted mortality rates 5-8X general population)

• Huge impact on quality of life

Mortality: reduced frequency of Scleroderma Renal Crisis - more pulmonary fibrosis

Steen and Medsger ARD 2007 66:940-4
Risk factors for poor outcome

- Diffuse skin involvement
- Proteinuria
- PAH
- Pulmonary fibrosis
- NYHA class 2
- Late onset Raynauds

Gurman et al ARD 2010
Red flag symptoms or signs in Raynauds

- Sudden and late onset
- Constitutional features
- Thickened skin
- Digital ulcers
- Rashes
- Calcium deposits
- Arthritis
- Dry eyes/mouth
- Apthous ulcers
- Hypertension
- Dyspnea
- Muscle weakness
- Swallowing difficulties
- GI disturbances
Management of specific aspects of SSc

- Raynauds
- Skin thickening
- Gastro-intestinal
- Pulmonary fibrosis
- Pulmonary hypertension
- Renal crisis
Raynauds: Non pharmacologic

• Smoking cessation and avoiding the cold
• Creams to moisturise dry skin can also help
• Avoid drugs such as
  – Beta blockers
  – Ergotamine
  – Clonidine
  – Cyclosporin
  – Cocaine
Raynauds: Medical treatment

- **Calcium Channel blockers**
  - Nifedipine
  - Nicardipine
  - Amlodipine 10-20mg daily
  - Diltiazem

- **Alpha blockers**
  - Prazocin

- **Angiotensin Receptor blockers**
  - Losartan 50-100mg od

- **Prostacyclins (IVI)**
  - Alprostadil
  - Iloprost

- **PDE5 inhibitors:**
  - Sildenafil 100mg od
  - Tadalafil 40mg od

- **Sympathectomy – digital vs axillary**
Skin manifestations of SSc

• Pruritis
  – Antihistamines (high doses)

• Skin thickening
  – Pentoxyfilline 400mg tid
  – Methotrexate up to 25mg po or sc weekly
# Treatment of GI manifestations

<table>
<thead>
<tr>
<th>Feature</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>GERD</td>
<td>Conservative measures PPI – high doses</td>
</tr>
<tr>
<td>GAVE (Watermelon stomach)</td>
<td>Laser photocoagulation Transfusions</td>
</tr>
<tr>
<td>Gastroparesis Pseudoobstruction</td>
<td>Domperidone 20mg tid Octreotide25-50mcg bid IV Erythromycin Pyridostigmine</td>
</tr>
<tr>
<td>Bacterial overgrowth</td>
<td>Cyclical antibiotics</td>
</tr>
<tr>
<td>Constipation</td>
<td>Laxatives</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Codeine</td>
</tr>
<tr>
<td>Incontinence</td>
<td>Sacral nerve stimulator</td>
</tr>
</tbody>
</table>
Treatment of Pulmonary fibrosis

- Cyclophosphamide oral (2mg kg day) or IV (600mgm2) – only drug shown to be effective in RCT
  - Modest improvements in FEV1 and TLC and dyspnea scores
  - Significant improvement in CT appearances
  - Improvements in skin scores
  - Benefits lasted 6 months after stopping Cyc
  - Most benefit in patients with worse baseline CT findings

Tashkin et al 2007 AJRCCM 176:1026
Hoyles et al 2006 A&R 54:3962
12 months oral cyclophosphamide: Sustained improvement at 18 months

P=0.364
Recommendations

• Cyclophosphamide IV (500-750mg/m²) for 6-12 months
• On completion, switch to oral MMF 2-3g per day or AZA 2-3mg per kg per day for several years

Pulmonary Hypertension Algorithm

TT ECHO

- RVSP ≤ 35mmHg
  - Unlikely PAH

- RVSP 35-40mmHg
  - No dyspnoea
  - Dyspnoea

- RVSP ≥ 40mmHg
  - Suspect PAH
  - Right Heart Catheterisation
Pulmonary Hypertension: treatment

- Improved survival in PAH
- Supportive therapies:
  - Oxygen (if resting pO2 under 60mmHg)
  - Loop diuretics
  - Digoxin
  - (anticoagulation)
- Calcium channel blockers (after dynamic testing)
- IV epoprostenol
- Endothelin receptor antagonists – Bosentan, Ambrisentan-
  improved exercise capacity and functional status
- PDE5 inhibition- Sildenafil, tadalafil – improved exercise capacity
Renal Crisis

- Increasing BP
- Microangiopathic hemolytic anemia
- Rising Creatinine

- ~25% mortality in 1 year
- 20 to 50% risk of developing end-stage renal disease
  - 2 year mortality 50% (vs 36% in non-scleroderma dialysis)

Management
- Monitor BP and creatinine
- Careful with dose of oral steroids
- ACE-I – Captopril 12.5mg tid increasing aggressively

Steen et al 2005 J Rheum
Part 1: Take Home Messages

- Consider SSc in:
  - new onset Raynauds
  - Raynauds in older patient
- Monitor for pulm fibrosis with annual PFTs and treat with cyclophosphamamide
- Monitor for PAH with annual ECHO refer for RHCath if pressures $\geq 40$ and dyspnoeic
- Beware of steroid dose in SSc – $\geq 15$mg may precipitate Scleroderma Renal Crisis (SRC)
- Monitor BP and creatinine carefully esp in diffuse disease
- Multisystem disease: Talk to colleagues...
What’s new in scleroderma

• Guidelines
• Antibodies
• Immunological and genetic studies
• Treatments
• Stem cell transplant
Objective:

• To increase sensitivity and specificity relative to 1980 classification
• To ensure inclusion in studies of all appropriate patients with SSc particularly those with early SSc or limited cutaneous disease
• To include disease manifestations of 3 major aspects and advances in diagnosis:
  – Vasculopathy
  – Fibrosis
  – Antibody Production
## 2013 ACR/EULAR SSc guidelines

<table>
<thead>
<tr>
<th>Item</th>
<th>Sub-item</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin thickening of fingers of both hands extending proximal to MCP joints (sufficient criterion)</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>Skin thickening of fingers <em>(only count higher score)</em></td>
<td>Puffy fingers Sclerodactyly of fingers (distal to MCP joints but proximal to PIP joints)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Fingertip lesions <em>(only count higher score)</em></td>
<td>Digital tip ulcers Fingertip pitting scars</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>

Van den Hoogen 2013
### 2013 ACR/EULAR SSc guidelines

<table>
<thead>
<tr>
<th>Item</th>
<th>Sub-item</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal nailfold capillaries</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary arterial hypertension and/or interstitial lung disease</td>
<td>Pulmonary arterial hypertension</td>
<td>2</td>
</tr>
<tr>
<td><em>(maximum score is 2)</em></td>
<td>Interstitial Lung Disease</td>
<td>2</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>SSc-related autoantibodies (anticentromere, anti-RNA polymerase III, anti-topomerase I [anti-SCl-70] <em>(Maximum score is 3)</em></td>
<td>Anti-centromere</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Anti-topomerase I</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anti-RNA polymerase</td>
<td></td>
</tr>
</tbody>
</table>

Total score = Sum of maximum score in each category
Total Score ≥ 9 Classified as Definite SSc; Maximum Score is 19
2013 ACR/EULAR SSc guidelines

- Classification criteria for SSc **not applicable** to patients with
  - skin thickening sparing fingers
  - scleroderma-like disorders better described by other conditions (e.g. nephrogenic sclerosing fibrosis, generalized morphea, eosinic fasciitis, etc.)
Strengths of 2013 Classification System

• More inclusive and identifies patients with early disease (≤ 3 yrs)
• Greater specificity (0.92 vs 0.72) and sensitivity (0.91 vs. 0.75) relative to 1980 classification
• Easy to administer
• Includes recent advances:
  – Autoantibodies with opportunity to add others
  – Magnified nailfold visualization (ophthalmoscopes, dermatoscopes or videocapillaroscopy cameras)
Limitations of New Classification System

• **Identifies only a subset of patients diagnosed with SSc** as it does not use some items useful for diagnosis:
  - Calcinosi, flexion contractures of fingers, tendon or bursal friction rubs, renal crisis, esophageal dilation, dysphagia
  →Reason- do not improve sensitivity and specificity
• Ideally diagnosis and classification criteria would be the same
• As no gold standard exist for defining a SSc pt, used 2 sources of expert opinion (and data): (1) Clinician who chose pts for derivation and validation samples & (2) group of expert clinicians on SSc: Possibility of selection bias & differing opinions/sources of information
# Auto-Antibodies

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Rate in Disease Subset</th>
<th>Clinical Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Topomerase I</td>
<td>60.8% (DcSc) 6.0% (LcSSc)</td>
<td>High modified Rodnan skin score (mRss), joint &amp; muscle involvement, GI involvement, cardiomyopathy, hypertension, proteinuria, pulmonary fibrosis (in absence of ACA)</td>
</tr>
<tr>
<td>Anti-centromere</td>
<td>23.4% (DcSSc) 46.7% (LcSSc)</td>
<td>Correlated with longstanding RP and SSc, associated with calcinosis, RP, esophageal motility, sclerodactyly, telangiectasia (CREST) SSc, lower likelihood of pulmonary fibrosis (in absence of anti-topo I).</td>
</tr>
<tr>
<td>Antibody</td>
<td>Rate in disease subset</td>
<td>Clinical Characteristics</td>
</tr>
<tr>
<td>------------------------</td>
<td>------------------------</td>
<td>------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Anti-fibrillin-I</td>
<td></td>
<td>Severe skin and systemic involvement and higher mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-activates fibroblasts and stimulates TGF-β</td>
</tr>
<tr>
<td>Anti-nucleolar</td>
<td></td>
<td>Mild, limited disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-target subclass of ribonuclear proteins U3-RNP &amp; fibrillarin</td>
</tr>
<tr>
<td>Anti-Th/To</td>
<td></td>
<td>Mild, limited disease</td>
</tr>
<tr>
<td>RNA Polymerase III</td>
<td>10-20% in SSc cohorts</td>
<td>Severe skin disease, scleroderma renal crisis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Co-temporal SSc &amp; cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-unique expression of RNAPIII in malignant tissue</td>
</tr>
</tbody>
</table>
Functional Antibodies

• Anti-ET-A receptor Antibody
  – Bind respective receptors on endothelial cells
  – ↑ TGF-β (pro-fibrotic cytokine)
  – Correlated with SSc severity and mortality

Riemekasten et al 2011
Candidate Gene and GWAS studies

• 2 approaches for identification of genetic loci related to disease susceptibility:
  
  – **Genome-wide association studies (GWAS):** Scan genome with tag to identify single nucleotide polymorphisms (SNPs)
    → can identify novel genes
  
  – **Candidate gene studies:** SNPs in suspected disease-related genes tested in case-control comparison
    → can test for gene with known functional consequences
GWAS

• HLA genes
  • HLA DPB1*1310 associated with anti-topoisomerase 1 (OR 14)
  • HLA DRB1*1302 associated with anti-fibrillarin (OR 6)

• Non-HLA genes
  – Immune processing
  – Antigen presentation
  – Inflammation
  – Immune signalling (STAT4)
  – Innate immunity (IRF5)

Endothelial Injury in TGF-β-Dependent Mouse Model of Scleroderma

• Kinase-deficient TGF-β receptor type II mouse strain → upregulation of TGF-β signaling → Replicates fibrotic features of SSc:
  – Vasculopathy with medial thickening
  – Perivascular proliferating chronic inflammation
  – Mildly elevated pulmonary artery pressure (PAH)

• VEGF inhibition (SU5416) enhanced the vasculopathy:
  – Pulmonary arteriolar lumen obliterated by apoptosis-resistant proliferating endothelial cells → RV hypertrophy and significant PAH

• Double hit theory

EC Derrett et al 2013
Endothelial Injury in TGF-β-Dependent Mouse Model of Scleroderma

A-E Representative pulmonary arteriole sections from transgenic and wild-type mice, stained with H&E (A&B), picrosirius red, elastin van Gieson (D) and α-smooth muscle actin (E)
Endothelial Injury in TGF-β-Dependent Mouse Model of Scleroderma

• In advanced SSc-related PAH  \( \uparrow \) \textbf{VEGF levels} accompany dysregulated angiogenesis
  – May reflect abnormal repair mechanism

• Model may relate to SSc-related PAH: alteration in TGF-β and VEGF signaling in pulmonary circulation & structural vasculopathy resembling murine chronic hypoxic PH

• Consider targets for therapy in SSc-PAH
Anti-fibrotics

- Difficult to assess antifibrotic effect of medications in RCTs due to natural disease progression

<table>
<thead>
<tr>
<th>Drug</th>
<th>Current evidence</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillamine</td>
<td>Randomized, uncontrolled multicentre trial, Skin scores decreased in high and low dose groups – no significant difference&lt;br&gt;Retrospective study, median dose 750 mg/day stat sig improvement on skin and internal organ involvement</td>
<td>Clements</td>
</tr>
<tr>
<td>Colchicine</td>
<td>Uncontrolled studies, contradictory results, no RCTs</td>
<td>Segovia Guttadauria</td>
</tr>
<tr>
<td>Minocycline</td>
<td>Open-label multicentre trial - No benefit</td>
<td>Mayes</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>RCT, some improvement in skin scores and significant increase in mouth opening</td>
<td>Grasseger</td>
</tr>
<tr>
<td>IFNα</td>
<td>RCT, no benefits, side effects common</td>
<td>Black et al</td>
</tr>
</tbody>
</table>
## New Treatments: Anti-fibrotics

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<thead>
<tr>
<th>Drug</th>
<th>Current evidence</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phototherapy</td>
<td>RCT, Phospheresis, modest benefit</td>
<td>Knobler et al</td>
</tr>
<tr>
<td>Relaxin</td>
<td>RCT, benefit at 25µmg/kg but not 100µg/kg, suggests narrow therapeutic index</td>
<td>Seibold</td>
</tr>
<tr>
<td>Halofuginone</td>
<td>Inhibits Collagen–I and MMP-2 Topical, encouraging results at 3 months</td>
<td>Pines</td>
</tr>
<tr>
<td>Ximedon</td>
<td>Controlled study, 56 pts, delivered electrophoretically, improved skin sclerosis</td>
<td>Salikhov</td>
</tr>
<tr>
<td>Pirfenidone</td>
<td>Inhibits fibroblast proliferation, TGF-beta Idiopathic pulmonary fibrosis, significant difference in vital capacity</td>
<td>Taniguchi Simone</td>
</tr>
</tbody>
</table>
# Raynauds therapies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical Evidence</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pentoxyfilline</td>
<td>1 open-label 24-wk study in 12 SSc pts showed significant reduction in skin scores. 2pt starting trial with ulcer were healed. 1 open label study with 220 pt showed improvement in microcirculation and reduction in TNFα</td>
<td>De Souza</td>
</tr>
</tbody>
</table>

Neiko
# New Treatments: Immunomodulators

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<thead>
<tr>
<th>Drug</th>
<th>Clinical evidence</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>3 RCTs, improved skin scores, no clear benefit to other body systems</td>
<td>Das Van den Hoogen Pope</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>Anti-IL-6 agent&lt;br&gt;2 Reported cases - softening of skin in 2 DcSSc pts (monthly, x6 months)</td>
<td>Yoshihito</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Case reports, small studies and 1 small RCT suggest benefit in skin sclerosis and lung disease</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>2 RCTs (1 oral, 1 IV) –benefit in SSc-ILD and improved skin scores</td>
<td>Tashkin Hoyles</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>Benefit in small studies, larger studies required</td>
<td>Karleen su</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>No RCTs of azathioprine alone but recommended in maintenance therapy and cyclophosphamide</td>
<td>Hoyles Berezne</td>
</tr>
<tr>
<td>Mycophenolate mofentil</td>
<td>1 large retrospective and 1 prospective study - benefit in skin sclerosis and lung disease</td>
<td>Nihtyanova Swigris</td>
</tr>
<tr>
<td>Calcineurin inhibitors (Cyclosporin, Tacrolimus)</td>
<td>Showed benefit in skin sclerosis but abandoned due to side effects</td>
<td>Clements Filaci</td>
</tr>
</tbody>
</table>
# New Treatments: Immunomodulators

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<tr>
<th>Drug</th>
<th>Clinical Evidence</th>
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<tbody>
<tr>
<td>TNFα inhibitors</td>
<td>Studies demonstrate benefit in SSc-related arthritis; may benefit inflammatory stage of fibrotic/overlap disease</td>
<td>Lam Denton Plumethum</td>
</tr>
<tr>
<td>IV Immunoglobulin</td>
<td>Uncontrolled studies – benefit in skin scores</td>
<td>Levy Nacci</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>1 study showed positive changes in blood mononuclear profile, but no clinical benefits shown</td>
<td>Carbone</td>
</tr>
</tbody>
</table>
# New Treatment: Targeted Therapies

<table>
<thead>
<tr>
<th>Target</th>
<th>Clinical Evidence</th>
<th>Reference</th>
</tr>
</thead>
</table>
| Anti-TGF-β   | TGF-β has central role in SSc pathogenesis  
Metelimumab 0.5, 5 and 10 mg/kg versus placebo  
-No clinical benefit and serious side effects including death | Denton                     |
| Anti-PDGF    | Fli 1 is deficient in SSc and may be involved in vasculopathy and has role in collagen I repression and inhibition of TGFβ profibrotic gene programme  
Imatinib mesylate reverses expression levels of Fli 1 and suppresses collagen I production in SSc fibroblasts.  
Improves PAH in animal models, case reports and small phase II clinical trial;  
Small open label phase II study (30 pt) reported Improved Skin Score, FVC, and diffusion capacity in 17 evaluable pts. But 10 pt proof of concept study showed poor tolerance and no skin improvement | Schermuly Ghofrani  
ACR 2009 Abstract 606 |
# New Treatment: Targeted Therapies

<table>
<thead>
<tr>
<th>Target</th>
<th>Clinical Evidence</th>
<th>Reference</th>
</tr>
</thead>
</table>
| Rho Kinase Inhibitors   | Rho kinase (Rock) reorganizes actin cytoskeleton and triggers contraction of smooth muscle: may stimulate differentiation of fibroblast to myofibroblasts.  
Fasudil under investigation for use in RP  
Antifibrotic effect of statins may be mediated through ROCK inhibition; 84 pts in RP secondary to Ssc randomized to atorvastatin or placebo; at 4 months significant improvement in VAS, DU severity and pain scales, VAS for physician global assessment and endothelial markers of activation | Abou-Raya     |
| PPAR\(\gamma\)          | PPAR\(\gamma\) limits duration and intensity of fibroblast activation  
PPAR\(\gamma\) agonist, rosiglitazone caused reduction in type I collagen, connective tissue growth factor and smooth muscle actin in 5 dcSSc pts                                                                 | Shi-wen       |
New Treatments- Stem Cell Transplantation

- 2 randomized Phase III trials on HSCT

    ASTIS (Europe)        SCOT (North America)

    156 pt

    Recruitment completed in 2011

    Primary endpoint: Event-free survival

    Result: Better event-free and overall survival (time varying hazard ratio p=0.002)

    Deaths: 40 (16 HSCT/24 control)

    Primary Endpoint: Global Rank Composite Score at 54 mo: pt’s order relative to other pts in terms of death, event-free survival FVC, Scleroderma HAQ, mRss

Sullivan KM, Muraro P, Tyndall A. 2010 Biol Blood Marrow Transplant
New Treatments- Stem Cell Transplantation

• Hematopoietic stem cell transplantation (HSCT) after immune ablation allows immune system to “reset”, stops fibrotic process and eliminating auto-antibody-producing plasma cells
• 1/3 of 170 transplanted SSc pt experienced sustained remission
• 81% of 26 pt with autologous stem cell transplant for severe DcSSc had clinical response at median F/U at 5.3 years
• Survival rates at and event-free survival 5 and 7 years were 96.2% & 84.8% and 64.3 % and 57.1% respectively (Vonk 2008)
New Treatments- Stem Cell Transplantation

• HSCT has offered rapid and sustained improvements in skin thickening and functional ability, stabilizing organ function and possible improved VC and lung disease assessed by HRCT

• Mesenchymal cells are promising candidates as immunomodulatory agents – low toxicity, no need for ablation of immune system: One SSc pt with critical limb ischemia was transplanted with blood flow restored and skin necrosis reduced
Take home messages: Part 2

• GWAS studies have identified several immunological targets
• Newer treatment strategies target some of these mechanisms
• Stem cell transplantation shows promise
Hamilton Scleroderma Group

Established following a grant of $450,000 from the Scleroderma Society of Ontario in 2010

Improved access & clinical care for patients with SSc and Collaborative research

• A model of *comprehensive care*
Collaborations

• Cardiology – Dr Kitching and Dr Valettas

• Respirology – Dr Cox and Dr Kolb, Dr Amer, Dr Mann

• GI – Dr. Ganguli, Dr Mazzadi

• Nephrology – Dr. Margetts

• Dermatology – Dr Vignjevic

• Wound care – Dr Mayer

• Immunology – Dr Larché, Dr Denburg

• Nursing support – Ellen McDonald

• SSO – Maureen Sauvé
Hamilton Scleroderma Group and the CSRG

• 16 collaborating rheumatologists across Canada
• Around 1600 patients recruited since 2004 (150 from Hamilton)
• Low refusal rate for patients
• 86% females
• Average age = 55 y.o. ± 12 y.
• About 87% fulfill the ACR Criteria for Scleroderma
• Mean number of years since onset of non-Raynaud’s symptoms: 10.9 ± 9.0
• Mean number of years since diagnosis of SSc: 8.0 ± 8.0
• Positive for ACR criteria: 88.2%
• Limited: 59.1%        Diffuse: 37.7%        SINE: 3.1%
Conclusions

• Discussed
  – Clinical features
  – Current treatment strategies
  – New advances
  – Hamilton experience

• Thanks to HSG collaborators, rheumatology colleagues, Dr Russell